Reply to Van de Wijer et al

TO THE EDITOR—We thank Van der Wijer et al [1] for their interest in our study [2]. We agree that efforts to improve pediatric human immunodeficiency virus (HIV) treatment must optimize health outcomes and quality of life from childhood through-out adolescence and into adulthood. Thus, weighing potential toxicities and side effects along with the benefits of each regimen requires careful consideration. Our study randomized nevirapine-exposed HIV-infected children ≥ 3 years of age who were virally suppressed on a lopinavir/ritonavir (LPV/r)-based regimen to either switch to an efavirenz (EFV)-based regimen or remain on LPV/r; after 1 year of clinical trial follow-up [3], participants were invited into a prospective observational study and we reported outcomes over a median of 46 months from randomization [2].

Van der Wijer and colleagues noted the concerning central nervous system symptoms associated with EFV in adults, and the limited data on this association in children [1]. Our own concerns about this led us to collect standardized data on sleep and the Strengths and Difficulties Questionnaire (SDQ) [4] during the clinical trial [3]. While more children randomized to EFV (26%) than those who remained on LPV/r (0%) reported nightmares or trouble sleeping 4 weeks after randomization, these sleep disturbances resolved by the next visit, with no differences observed between arms at bimonthly visits from 8 through 48 weeks. Furthermore, we administered the SDQ at weeks 4 and 48 and did not observe significant differences in any category or the total score at either visit (Table 1). We previously reported 4 cases of EFV-related neurotoxicity, including 2 cases of seizure disorder within this cohort, 1 outside the trial, and 1 case of cerebellar dysfunction in the cohort [5, 6]. Over >5 years of follow-up, we have not observed any further central nervous system symptoms in children on EFV.

In our cohort, few children experienced virologic failure (plasma HIV RNA >1000 copies/mL, confirmed) and this risk was comparable across arms. However, in children randomized to EFV, lower-level viremia (plasma HIV RNA 50–1000 copies/mL) was less frequently observed and caregiver-reported adherence was superior. The poor palatability of the liquid formulation of LPV/r can present a significant challenge for caregivers, and the large size of the solid formulation also poses challenges for children still learning to swallow tablets. These burdens on caregivers of younger children are considerable. As children enter adolescence, any measure that mitigates adherence barriers could have an important impact on treatment success. Notably, once-daily regimens, available with EFV, can strengthen adherence [7].

An estimated 43% of 2.1 million children living with HIV in 2016 accessed antiretroviral treatment (ART) [8]. Streamlined ART scale-up is critical to reduce long-term morbidity and mortality in children living with HIV. Among children randomized to EFV, we observed superior virologic control and improved lipid profiles. Moreover, EFV is beneficial for children requiring tuberculosis treatment, does not require cold-chain storage, harmonizes treatment with adult guidelines, and preserves second-line options. While awaiting access to pediatric formulations of antiretrovirals in sub-Saharan Africa with fewer side effects, our data support the World Health Organization recommendation [9] to switch to EFV in conjunction with clinical and virologic monitoring in children ≥ 3 years of age.

Table 1. Strengths and Difficulties Questionnaire at 4 Weeks and 40 Weeks Postrandomization, by Arm

Category	Week 4			Week 40		
	Ritonavir-Boosted Lopinavir	Efavirenz	PValue	Ritonavir-Boosted Lopinavir	Efavirenz	PValue
No.	146	150		148	144	
Total difficulties score			.300			.912
Normal: 0–13	73 (51.1)	61 (42.4)		54 (38.3)	55 (40.2)	
Borderline: 14–16	26 (18.2)	34 (23.6)		31 (22.0)	31 (22.6)	
Abnormal: 17–40	44 (30.8)	49 (34.0)		56 (39.7)	51 (37.2)	
Emotional symptoms score			.946			.105
Normal: 0–3	79 (55.2)	80 (54.8)		71 (50.4)	56 (40.6)	
Borderline: 4	27 (18.9)	26 (17.8)		20 (14.2)	32 (23.2)	
Abnormal: 5–10	37 (25.9)	40 (27.4)		50 (35.5)	50 (36.2)	
Conduct problem score			.178			.792
Normal: 0–2	59 (41.3)	56 (38.9)		49 (35.8)	53 (38.7)	
Borderline: 3	11 (7.7)	21 (14.6)		20 (14.2)	18 (13.1)	
Abnormal: 4–10	73 (51.1)	67 (46.5)		72 (51.1)	66 (48.2)	
Hyperactivity score						.428
Normal: 0–5	91 (63.6)	83 (56.9)	.484	75 (53.2)	84 (60.9)	
Borderline: 6	31 (21.7)	39 (26.7)		46 (32.6)	37 (26.8)	
Abnormal: 7–10	21 (14.7)	24 (16.4)		20 (14.2)	17 (12.3)	
Peer problem score			.495			.879
Normal: 0–2	73 (51.1)	67 (45.9)		65 (46.1)	64 (46.4)	
Borderline: 3	19 (13.3)	17 (11.6)		12 (8.5)	14 (10.1)	
Abnormal: 4–10	51 (35.7)	62 (42.5)		64 (45.4)	60 (43.5)	
Prosocial behavior score			.207			.189
Normal: 6–10	139 (97.2)	136 (93.8)		134 (95.0)	132 (95.7)	
Borderline: 5	3 (2.1)	3 (2.1)		5 (3.6)	1 (0.7)	
Abnormal: 0–4	1 (0.7)	6 (4.1)		2 (1.4)	5 (3.6)	

Data are presented as No. (%) unless otherwise indicated.

Notes

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Human Immunodeficiency Virus Medicine Association Pain Management Guidelines Needed to Curb Opioid Epidemic

TO THE EDITOR—We applaud the panel of experts for the well-written guideline on management of chronic pain in which nonpharmacological options for persons with human immunodeficiency virus (PWH) are discussed [1]. We have seen the benefits of these modalities in the integrative medicine program at our hospital practice for 17 years. Yoga, massage, and acupuncture, which are offered in our practice, have remarkably benefited patients with musculoskeletal conditions and neuropathic pain. In our experience, we have successfully withdrawn opioid therapy using nonpharmacologic therapies.

The guideline is extremely timely as addiction to opioids is a serious national crisis that affects public health, patient safety, and economic welfare. The Centers for Disease Control and Prevention estimates that the total economic burden of prescription opioid misuse in the United States is \$78.5 billion a year [2]. Recently, providers have been called on to curtail the use of opioids, and patients have been informed that their prescription medications will be tapered or discontinued. These nonpharmacologic therapies are often not available due to lack of coverage, especially by the federal- and state-supported programs that our patients heavily rely on. Most commercial insurance companies are not covering these treatments, and hospitals cannot support integrative medicine programs without external sources. Furthermore, experts

in modalities of integrative medicine are limited in the workforce, and more training specific to pain management for PWH is greatly needed. While physical therapy and cognitive-behavioral therapy may be covered for short periods of time, frequently those who provide these services lack expertise in human immunodeficiency virus (HIV) related conditions. It is critical that as care providers for PWH, we draw national attention to our patients' needs as new guidelines are being rolled out to improve pain management.

The 2017 chronic low back pain guideline by the American College of Physicians [3] states that physicians and patients should treat acute and subacute low back pain with nonpharmacologic therapies such as superficial heat, massage, acupuncture, and spinal manipulation. For patients with chronic low back pain, the recommendation is that physicians and patients also initially select nonpharmacologic therapy such as exercise, multidisciplinary rehabilitation, acupuncture, mindfulness-based stress reduction, tai chi, yoga, motor control exercise, progressive relaxation, electromyography biofeedback, low level-laser therapy, operant therapy, cognitive behavioral therapy, and spinal manipulation. We wholeheartedly agree with these recommendations and those of the HIV Medicine Association and implore coverage providers to support these therapies in order to curb the opioid epidemic. We intend to add these recommendations to our integrative medicine curriculum in order to educate providers and students in our hospital practice.

We propose that providers endorse and proactively engage their administrations to support use of nonpharmacologic therapies to control pain as this is in the best interest of our patients and society. We fear that without adequate support of these programs, providers may feel that they have no alternative but to continue to prescribe opioids, which would only fuel this epidemic. We have a national crisis at hand and the knowledge to curb it—now is the time to implement change.