resource-limited settings. Whereas PMTCT interventions in industrialized countries where breastfeeding is rarely practiced are truncated at the time of delivery, developing countries have to contend with postnatal transmissions as well. The authors hinged their hopes on results of the ongoing Breastfeeding, Antiretrovirals and Nutrition (BAN) and Kesho Bora studies to provide evidence that continuing cART during lactation could reduce the risk of postnatal HIV transmission.

My take is that we should extrapolate what we know about the relationship between ART and viral load changes in blood as well as in semen [9–10], without wasting too much time. The evidence that the two studies are supposed to generate should ideally be gathered in an operational research setting in which services can be concurrently provided. We cannot afford to investigate every body fluid before we put interventions into place if the HIV and AIDS pandemic is indeed a public health concern.

Finally, the point the authors made on the cost-effectiveness of HIV prevention does not need any belabouring. They estimated the cost of a first-line cART regimen in resource-limited settings at US$ 220 per annum. Estimations of the cost of life-long treatment for an HIV-infected individual are even more compelling, ranging between US$ 222, 852 and 389, 151 (2005 dollars) depending on the discount rate used [11]. The implication is that whatever resources are expended to avert HIV infections they are bound to be cost-effective down the road.

In conclusion, WHO is both the victim and the villain in equal proportions regarding the inconsistent PMTCT recommendations. It is a victim in the sense that the organization has no resources to ensure implementation of what it recommends. This results in a tendency to provide a menu from which every country/region can pick what is feasible within their contexts. On the contrary, WHO is a villain for not letting the end users of its recommendations know that these are proposals that should not be mistaken for law. Such openness is likely to encourage more developing countries to go the Brazilian way of making provision of standard healthcare to the citizenry a national priority. Without taking such bold steps, the HIV and AIDS pandemic is quickly evolving into a third world epidemic.

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Givans Kay Ateka, *Irish Aid, Maseru, Lesotho.*

Correspondence to Dr Givans Kay Ateka, Irish Aid, Private Bag A67, Maseru 100, Lesotho.
Tel: +26622314068; e-mail: Givans.Ateka@dfa.ie

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Substituting nevirapine for efavirenz: risk factors for toxicity in nonnaive patients in a resource-constrained setting

We read with interest the paper by Kesselring *et al.* [1], reporting on the risk factors for treatment-limiting nevirapine (NVP)-associated toxicity in antiretroviral treatment (ART)-naive and experienced patients in Europe. Whereas various studies from resource-constrained settings (RCSs) have focused on risk factors for NVP-related toxicity in ART-naive patients, little is known on the risks of initiating NVP in ART-experienced patients, in particular after

ART-induced CD4 cell count increases. As it is custom to substitute NVP for efavirenz (EFV) after tuberculosis treatment, this is an important operational question in RCSs, in which rates of HIV/tuberculosis coinfection are high. Kesselring *et al.* report on the association of a detectable viral load and an increased risk of hypersensitivity reactions (HSRs) in treatment-experienced patients. Given the limited availability of viral load testing in RCSs, we aimed to identify risk factors for NVP toxicity for patients substituting NVP for EFV in our program in Cambodia, focusing on clinical information that is readily available in these settings.

In 2003, we started providing ART in a private not-for-profit hospital in Phnom Penh, Cambodia, with NVP-containing fixed drug combinations as preferential first-line regimen [2]. In case of tuberculosis, EFV was used instead of NVP, with the recommendation to revert to NVP (at some point) after the end of tuberculosis treatment. We assessed the risk of HSRs in 173 ART-experienced adult patients, substituting NVP for EFV. They were predominantly men (62%) and generally presented with advanced HIV disease [nadir CD4 count of 43 cells/μl; interquartile range (IQR) 15–111)]. NVP was substituted a median of 14 months (IQR 8–26) after starting ART, with a median CD4 cell count of 235 cells/μl (IQR 154–370) at the time of NVP initiation (Table 1). In total, 19 (10.9%) patients developed a treatment-limiting HSR within the first 6 months after substitution, of whom nine presented with hepatotoxicity and 10 with skin rash. Toxicity occurred at a median time of 22 days (IQR 14–31) after NVP initiation. Whereas female sex or high nadir CD4 cell count was not independently associated with HSRs, higher CD4 cell counts at the time of NVP substitution increased the risk of subsequent NVP toxicity (Table 1). In addition, longer duration of ART prior to NVP initiation appeared to protect against NVP toxicity. Similar findings were found when exploring different CD4 cell count cut-offs for women and men; no significant interactions were detected.

The cumulative incidence of severe HSRs of 10.9% in this analysis in ART-experienced patients is comparable with the incidence of 8.2% in ART-naive patients in our program (data not shown). A similar estimate for ART-experienced patients was obtained in another study in Cambodia [3]. Despite the higher CD4 cell counts, ART-experienced Cambodians appear to have a risk of NVP toxicity comparable with that of ART-naive patients. The observed association with CD4 cell count at the time of NVP substitution is in agreement with the findings of Kesselring *et al.* [1]. In line with others [4], but in contrast to their findings [1,5], no independent association of HSRs with nadir CD4 cell count for ART-experienced patients was observed. However, the relatively small sample size and the generally low nadir CD4 counts in our study should be taken into consideration. We note that we did observe a positive association of HSRs with nadir CD4 count in our ART-naive population (data not shown). The association of HSRs with duration of ART treatment prior to NVP substitution is a new finding. Whether this relates to the reduced risk of HSRs associated with suppressed HIV viremia, as reported by Kesselring *et al.* [1], or with a protective effect of lesser immune hyperstimulation [6,7], remains to be explored.

The present study has several limitations. First, the study has all the intrinsic limitations of a retrospective analysis. As it is up to the clinician to decide whether to replace

Table 1. Risk factors associated with nevirapine-related toxicity in treatment-experienced patients ($N = 173$).

	HSR N (%)[a]	HR[b]	P	Adjusted HR[b,c]	P
Female sex	10/65 (15.4)	1.9 (0.8–4.6)	0.17		
Age >35 years	15/110 (13.6)	2.2 (0.5–6.6)	0.16		
Baseline WHO III/IV	17/155 (11.0)	1.0 (0.2–4.2)	0.96		
Nadir CD4 count					
≤50 cells/μl	8/89 (9.0)	1	0.13		
50–250 cells/μl	9/69 (13.0)	1.5 (0.6–3.9)			
>250 cells/μl	2/8 (25.0)	3.2 (0.7–15.0)			
CD4 cell count at NVP substitution					
≤250 cells/μl	5/75 (6.7)	1	0.09	1	0.01
250–400 cells/μl	8/62 (12.9)	2.0 (0.7–6.3)		2.8 (0.9–8.7)	
>400 cells/μl	6/36 (16.7)	2.7 (0.8–8.9)		4.6 (1.3–16.0)	
Time on ART at NVP substitution					
≤1 year	10/71 (14.1)	1	0.18	1	0.03
1–2 years	6/52 (11.5)	0.8 (0.3–2.2)		0.6 (0.2–1.7)	
>2 years	3/50 (6.0)	0.4 (0.1–1.5)		0.2 (0.1–0.9)	
Hepatitis B coinfection	2/15 (13.3)	1.3 (0.3–5.5)	0.75		
Hepatitis C coinfection	1/4 (25.0)	3.5 (0.5–26.3)	0.23		
ALAT > ULN at NVP substitution	6/39 (15.4)	1.7 (0.6–4.6)	0.27		

ALAT, alanine aminotransferase; ART, antiretroviral treatment; HSR, hypersensitivity reaction (skin rash or hepatotoxicity); NVP, nevirapine; ULN, upper limit of normal values.
[a]Values are expressed as N with HSR/total N; the percentage is given in brackets.
[b]HR, hazard ratio; 95% confidence interval in brackets.
[c]Multivariate Cox regression model using backward selection method retaining covariates with $P < 0.05$.

EFV with NVP, indication bias cannot be excluded. Viral load measurements could have helped to clarify the association of time on ART and HSRs. Finally, the sample size of the study was relatively limited. Consequently, our findings need to be reassessed in larger studies and in different settings.

Identification of risk factors could contribute to informed decision-making. Based on these, clinical prediction rules could be developed for NVP substitution in ART-experienced patients, integrating besides NVP toxicity, issues like cost, pill burden and adherence. While awaiting wider access to viral load testing, time on ART at NVP substitution could be explored as a predictor for HSRs in RCSs.

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Johan van Griensven[a], Phally Un[b], Thong Phe[b], Sopheak Thai[b] and Lutgarde Lynen[a], *[a]Institute of Tropical Medicine, Antwerp, Belgium, and [b]Department of Infectious Disease, Sihanouk Hospital Center of HOPE, Phnom Penh, Cambodia.*

Correspondence to Johan van Griensven, Institute of Tropical Medicine, Nationalestraat 155, 2000 Antwerp, Belgium.
Tel: +32 3 247 64 76; fax: +32 3 247 64 52;
e-mail: jvangriensven@itg.be

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