Brief Report

A Visual Dosing Aid for First-line Pediatric Antiretroviral Treatment in Resource-poor Settings

by Steven F. J. Callens,[a] Daniel Westreich,[a] Faustin Kitetele,[b] Jean Lusiama,[b] Nicole Shabani,[b] Tom Belhorn,[c] Robert Colebunders,[d] Frieda Behets,[a] *and* Annelies Van Rie[a]

[a]*School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

[b]*School of Public Health, University of Kinshasa, Kinshasa, Democratic Republic of the Congo*

[c]*Department of Pediatrics, Division of Pediatric Infectious Diseases and Immunology, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

[d]*University of Antwerp and Institute of Tropical Medicine, Antwerp, Belgium*

Summary

The visual dosing aid (VDA) was developed to facilitate dosing calculations in response to children's growth and weight during antiretroviral treatment. The theoretical accuracy of the VDA was assessed using anthropometric data from 55 children receiving care in the USA and 324 children in the Democratic Republic of the Congo. The VDA dose was similar to the WHO recommended dose. A potentially significant relative dosing difference of $\geq$20% occurred in <3% of children for NVP, AZT and d4T, but was observed in 20% for 3TC, overdosing being more frequent. The VDA compared well with generic pediatric fixed dose combination tablets. Results did not differ between sites. The VDA enables accurate dosing of pediatric ART in distinct populations and could facilitate roll-out of pediatric ART in resource-poor settings.

Key words: children, resource-poor setting, antiretroviral treatment, drug dosing.

To optimize pediatric dosing in resource-poor settings, relatively complicated drug-dosing tables have been developed [1, 2]. We propose a visual dosing aid (VDA) to further simplify pediatric dosing of first-line pediatric antiretroviral (ARV) treatment when using generic adult tablets and nonrefrigerated syrups. The VDA can be used to calculate the initial ARV dosing and to monitor the need to adjust ARV dosing in response to changes in the child's weight and/or height.

The development of a 2D visual dosing graph with colored dosing bands for five first-line ARV drugs [nevirapine (NVP; 200 mg/m^2) or lopinavir/ritonavir (LPV/RTV; 230 mg LPV and 57.5 mg RTV/m^2), stavudine (d4T; 1 mg/kg), lamivudine (3TC; 4 mg/kg), zidovudine (AZT; 240 mg/m^2)] consisted of two main steps. First, body surface area was calculated using the Mosteller formula [3]. Second, we developed an NVP-based and LPV/RTV-based VDA by creating colored bands for the first-line ARV drugs using commonly available drug formulations (Fig. 1). VDA doses can consist of syrups, tablets or a combination, thus facilitating the most accurate dosing possible.

The theoretical performance of the VDA was evaluated using anthropometric data from children receiving ART in the Democratic Republic of the Congo (DRC) and the United States. The study was approved by the University of North Carolina at Chapel Hill Institutional Review Board and the

Acknowledgements

We like to acknowledge Oliver Medzarisky for facilitating the data collection in the University of North Carolina at Chapel Hill.

Funding

Cooperative Agreement 422422-4 of the Centers of Disease Control, Atlanta, GA, USA; additional funding from an unrestricted educational training grant from the UNC-GlaxoSmithKline Center for Excellence in Pharmacoepidemiology and Public Health (to D.W).

Correspondence: Steven F. J. Callens, 2102-D McGavran-Greenberg Hall, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7435, USA. Tel.: + 1 919-966-7430; Fax: + 1 919-966-2089. E-mail <callens@email.unc.edu>

doi:10.1093/tropej/fmn095 Advance Access Published on 20 November 2008

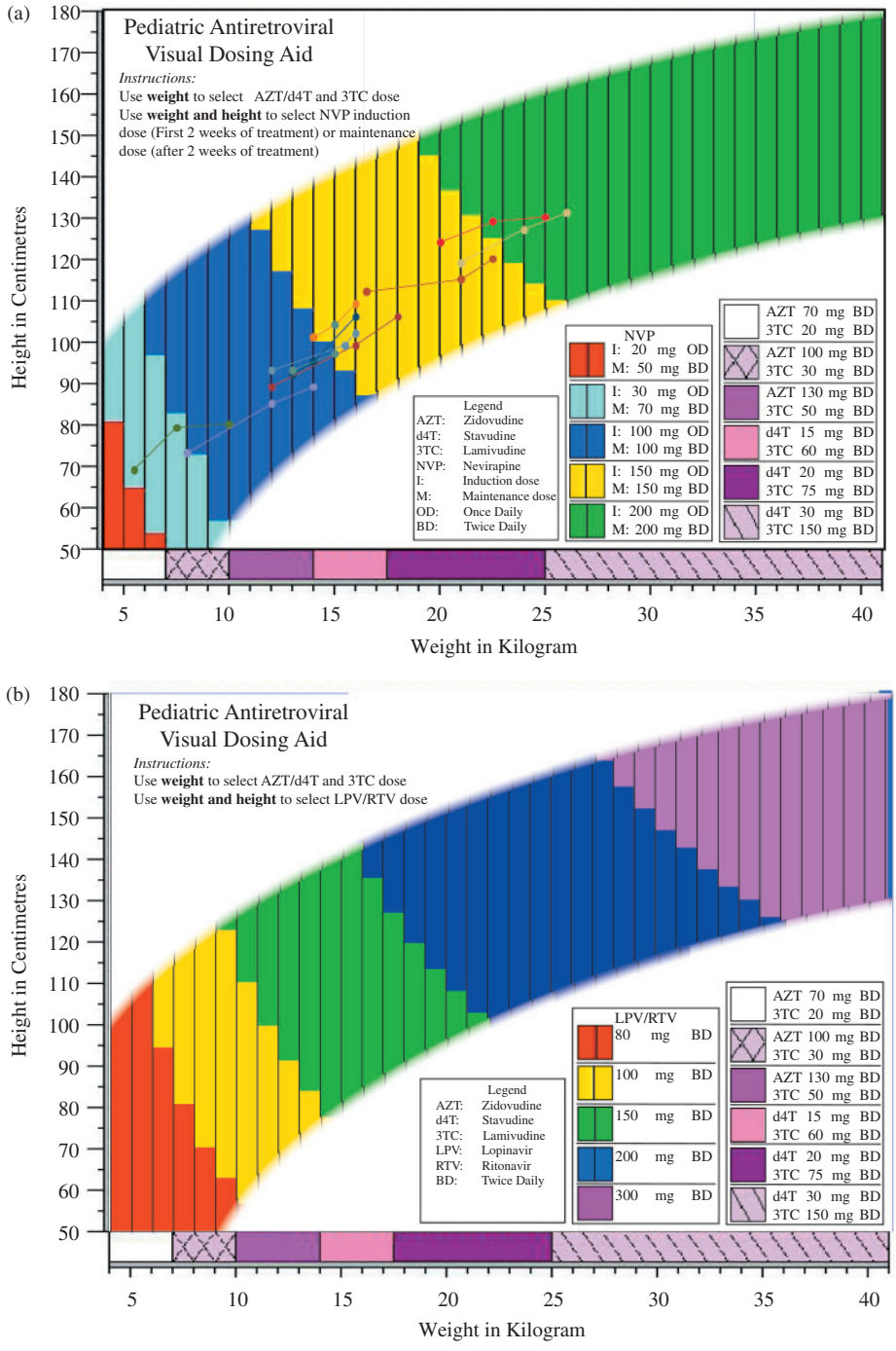

FIG. 1. Pediatric VDA [NVP (**A**) or LPV/RTV (**B**)]: ARV drug doses are obtained by graphing weight for AZT, 3TC and d4T, and weight and height for NVP. The ARV dose is obtained by looking up the corresponding color in the legend. The legend can be adapted to available formulations and expressed in milliliters, or amount of capsules or tablets. The lines plotted on the graph (A) represent the weight and height evolution of selected patients in the DRC at the start, after 6 and 12 months of ARV treatment.

TABLE 1
Distribution of the relative differences between VDA dose and WHO recommended dose by ARV drug

	d4T ($N = 200$)		AZT ($N = 179$)		3TC ($N = 379$)		NVP ($N = 379$)		LPV/RTV (N=379)	
Percentage (%)	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
>−20	0	0.0	1	0.6	15	4.0	0	0.0	0	0.0
Between −20 and −15	8	4.0	13	7.3	50	13.2	23	6.1	47	12.4
Between −15 and −10	26	13.0	24	13.4	33	8.7	42	11.1	5	1.3
Between −10 and 10	133	66.5	114	63.7	198	52.2	235	62.0	254	67.0
Between 10 and 15	18	9.0	22	12.3	15	4.0	51	13.5	15	4.0
Between 15 and 20	15	7.5	3	1.7	7	1.8	18	4.7	46	12.1
>20	0	0.0	2	1.1	61	16.1	10	2.6	12	3.2

Absolute difference defined as VDA dose minus the recommended dose, expressed in milligrams; relative difference defined as the absolute difference divided by the recommended dose, expressed in percentage.

Ethics Committee of the School of Public Health of the University of Kinshasa, DRC.

When using the VDA, the proportion of children receiving an over- or underdosing of possible biological importance (≥20% relative difference) did not exceed 3% for NVP, AZT and d4T (Table 1) [2]. In contrast, for 3TC, the difference between VDA and recommended dose was of possible biological importance in 20% of the children, with overdosing four times as frequent compared with underdosing. We believe that a risk of overdosing 3TC is preferable to underdosing NVP as data from pediatric studies of 3TC alone or in combination with other drugs have demonstrated that 3TC is safe, even at high doses [4–6]. There was no significant difference between the proportion of children with high absolute and/or relative dosing differences for any of the ARVs between the US and DRC site (Table 1). The LPV/RTV-based VDA performed similarly well as the NVP-based VDA.

The Triviro LNS kid FDC tablets (Ranbaxy, Gurgaon, Haryana, India) overdose d4T (median: +17.6%) and 3TC (25.0%), while NVP is underdosed (−3.7%). The proposed Pedimune tablets (Cipla, Mumbai, Maharashtra, India) underdose d4T (−6.2%) and NVP (−7.5%), while 3TC is overdosed (+25.0%). These dosing differences were all significantly larger when compared to the VDA dose.

Our research did not include assessment of drug levels, or virologic and immunologic outcomes. A prospective study assessing the risks of toxicity (due to overdosing), treatment failure risks (due to underdosing) and HCW dosing error rates would be necessary to validate the VDA further.

In conclusion, the newly developed user-friendly VDA results in accurate ARV dosing and could thus aid health care workers in determining the initial and follow-up ARV doses in children when using a combination of adult tablets and non-refrigerated syrups.

References

1. Ponnet M, Frederix K, Petdachai W, *et al*. A drug dosage table is a useful tool to facilitate prescriptions of antiretroviral drugs for children in Thailand. Int J STD AIDS 2005;16:420–6.
2. Weidle PJ, Abrams EJ, Gvetadze R, *et al*. A simplified weight-based method for pediatric drug dosing for zidovudine and didanosine in resource-limited settings. Pediatr Infect Dis J 2006;25:59–64.
3. Mosteller RD. Simplified calculation of body-surface area. New Engl J Med 1987;317:1098.
4. McKinney RE Jr, Johnson GM, Stanley K, *et al*. A randomized study of combined zidovudine-lamivudine versus didanosine monotherapy in children with symptomatic therapy-naive HIV-1 infection. The pediatric AIDS clinical trials group protocol 300 study team. J Pediatr 1998;133:500–8.
5. Lewis LL, Venzon D, Church J, *et al*. Lamivudine in children with human immunodeficiency virus infection: a phase I/II study. The national cancer institute pediatric branch-human immunodeficiency virus working group. J Infect Dis 1996;174:16–25.
6. Saez-Llorens X, Nelson RP Jr, Emmanuel P, *et al*. A randomized, double-blind study of triple nucleoside therapy of abacavir, lamivudine, and zidovudine versus lamivudine and zidovudine in previously treated human immunodeficiency virus type 1-infected children. The CNAA3006 study team. Pediatrics 2001;107:E4.