Journal of the Pediatric Infectious Diseases Society

ORIGINAL ARTICLE

Misclassification of Antiretroviral Treatment Failure Using WHO 2006 and 2010/2013 Immunologic Criteria in HIV-Infected Children and Adolescents in Western Kenya

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We evaluated treatment failure misclassification in human immunodeficiency virus–infected Kenyan children whose targeted viral loads were determined after suspected immunologic/clinical failure according to 2006 and 2010/2013 World Health Organization guidelines. The misclassification rate was 21% for the 2006 guidelines and 46% for the 2010/2013 guidelines, which supports current recommendations for routine viral load monitoring but not necessarily the proposed CD4 thresholds.

Keywords. failure; pediatric HIV; treatment.

INTRODUCTION

Worldwide, 3.2 million children <15 years old were living with human immunodeficiency virus (HIV) in 2013, and only 23% of those in resource-limited settings (RLS) received antiretroviral therapy (ART) [1]. Optimal ART monitoring in children in RLS has not been established yet. The 2013 World Health Organization (WHO) guidelines recommend routine viral load (VL) assessment as the preferred monitoring approach for diagnosing treatment failure; however, in settings in which this assessment is not feasible, the guidelines recommend using immunologic/clinical criteria [2].

Evaluations of the WHO immunologic/clinical monitoring strategies in adults found that they had low sensitivity and specificity for virologic failure determination [3, 4], which can lead to delayed failure identification and increased morbidity, death, and resistance accumulation. However, such monitoring can also lead to misclassification as failure and an early, unnecessary switch to valuable and expensive second-line therapy [3, 5].

Studies of nonvirologic monitoring using the 2010 WHO guidelines for children from South Africa [6] and our work from Cambodia [7] had findings similar to those in adults [4]. This is particularly important in children who are almost twice as likely to experience treatment failure in the first year of ART [5] and in children who are younger than 5 years, for whom ART initiation is now recommended regardless of clinical stage or CD4 count [2]. Furthermore, the implications of changing to second-line ART in children are considerable because of greater costs, poor tolerability, high pill burden, longer treatment time, fewer available formulations, and limited treatment options.

We assessed ART failure misclassification in children in western Kenya in whom first-line ART failure was suspected by their clinicians on the basis of WHO and local immunologic and clinical guidelines. We hypothesized that treatment failure-misclassification rates are high when the WHO guidelines are used.

METHODS

This retrospective observational study occurred at AMPATH (Academic Model Providing Access to Healthcare) in Eldoret, Kenya [8, 9]. During the study period, AMPATH provided clinical services to 8140 HIV-infected children (<17 years old), 4939 of whom were receiving ART [8, 9]. AMPATH guidelines directed clinicians to change to second-line therapy on the basis of WHO thresholds, which were modified in 2007 to include CD4 count decreases ≥30% over 6 months as an indication of failure [10]. Viral load measurements were limited at the time of the study [3]. In 2007, AMPATH guidelines were modified to recommend targeted VL assessment in children and adults with suspected immunologic/clinical failure on the basis of our results showing a high rate of failure misclassification in adults. The study was approved by US and Kenyan ethics committees.

Data on children in care between January 2006 (initial AMPATH VL testing) and January 2009 (study closure) were

Received 9 July 2015; accepted 1 February 2016; published online April 29, 2016.

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Journal of the Pediatric Infectious Diseases Society 2017;6(3):285–8

DOI: 10.1093/jpids/piw018

extracted from AMPATH records [11] on the basis of the following inclusion criteria: (1) HIV infection; (2) age 6 months to 17 years; (3) on first-line ART with zidovudine/stavudine, lamivudine, and nevirapine/efavirenz for ≥6 months; (4) VL result available after starting ART; and (5) CD4 count/percentage available within 60 days of the VL assessment.

We examined the diagnostic accuracy of WHO immunologic guidelines to predict virologic failure. The primary outcome measured was the percentage of subjects with concordance of measured VLs and predicted failure as defined by the WHO 2006 (in effect at the time of the study) and 2010/2013 immunologic monitoring guidelines. The 2006 WHO guidelines used immunologic failure thresholds of CD4 count <1500 cells/μl or CD4 percentage <25% for children up to 11 months of age; <750 cells/μl or <20%, respectively, in children aged 1 to 3 years; <350 cells/μl or <15%, respectively, in children aged 3 to 5 years; and <200 cells/μl or <15%, respectively, in children aged >5 years. The 2010 guidelines were modified to use a threshold CD4 count of <200 cells/μl or CD4 percentage of <10% in children aged 2 to 5 years and a CD4 count of <100 cells/μl in children aged >5 years [12]. The 2013 guidelines extended the use of CD4 count or CD4 percentage cutoffs of 200 cells/μl or <10%, respectively, to all children younger than 5 years, which is the rule we used (termed here the 2010/2013 guidelines [2]).

Virologic failure was defined as a VL of >400 copies/ml (assay threshold). The WHO guidelines were evaluated by using sensitivity, specificity, misclassification of treatment failure (ie, the proportion of patients classified as having experienced treatment failure according to immunologic criteria and had an undetectable VL out of all those who were classified as having experienced treatment failure [1-positive predictive value]), misclassification of treatment success (ie, the proportion of patients classified as having not experienced treatment failure according to immunologic criteria and had a detectable VL out of all those classified as having had treatment success [1-negative predictive value]), and accuracy (ie, the total proportion of correct predictions). Additional methods for obtaining diagnostic measures and an exploratory evaluation of better rule development are provided in the supplementary materials. Analyses were performed using R version 2.14.2.

RESULTS

A total of 103 patients <18 years old were included in this study (Table 1). On the basis of 2006 and 2010/2013 guidelines and CD4 counts, 63 (61%) of 103 children and 34 (33%) of 103 children, respectively, would have been classified as having experienced ART failure.

The overall failure-misclassification rates were 21% (22 of 103) with the 2006 guidelines and 46% (47 of 103) with the 2010/2013 guidelines Figure S1). On the basis of the 2006 guidelines, 6% (4 of 63) of the children classified as having experienced treatment failure were undetectable, whereas 45% (18 of 40) were misclassified as having had treatment success with a detectable VL; on the basis of the 2010/2013 guidelines, 6% (2 of 34) of the children classified as having experienced treatment failure were undetectable, whereas 65% (45 of 69) were misclassified as having had treatment success with a detectable VL. Two of the 3 children <2 years old, who were unclassifiable when the 2010 guidelines were used, were misclassified as having not experienced ART failure when the 2013 guidelines were used.

Only 2 of the study participants classified as having experienced treatment failure had a VL of 400 to 1000 copies/ml (713 and 627 copies/ml). Therefore, a reanalysis of the data with a VL threshold of 1000 copies/ml had little impact on our estimates and did not affect our conclusions.

Overall, the 2006 guidelines had higher sensitivity (77% vs 42%, respectively; $P < .001$) and accuracy (79% vs 54%, respectively; $P < .001$) than the 2010/2013 guidelines in identifying virologic failure (Table S1), but both guidelines had similar specificities (85% vs 92%, respectively; $P = .48$). An exploration of rule development found that a better rule may exist to classify treatment failure using age, ART duration, and CD4 values and trends (Table S2). The supplementary materials provide further results of this evaluation.

DISCUSSION

In this retrospective observational study of HIV-infected children and adolescents in western Kenya, the overall misclassification rates based on WHO immunologic guidelines for treatment failure prediction were 21% with the 2006 guidelines and 46% with the 2010/2013 guidelines. Most misclassification occurred for children erroneously classified as not having experienced treatment failure despite having a detectable VL, who would not have been switched to second-line therapy using immunologic criteria alone. The results of this study highlight the poor sensitivity and accuracy of currently used pediatric immunologic thresholds in predicting virologic failure. It is encouraging to note that in this patient population, of the children predicted to experience treatment failure on the basis of immunologic guidelines, the immunologic cutoffs were relatively specific.

The results of our study, for which the 2013 guidelines in children were used for the first time, are consistent with those of previous studies in adults [3, 4] and existing reports of studies in children [4, 6, 7]. Although limited by various definitions of immunologic failure and small sample sizes, the literature suggests consistently poor sensitivity of immunologic criteria for treatment failure prediction.

Previously published adult data revealed a predominance of failure misclassification for those with an undetectable VL [3, 4], in contrast to our data, which reflect a predominance of

Table 1. Demographic, Clinical, and Laboratory Characteristics of the Study Cohort According to Viral Load

Characteristic	VL ≤ 400 copies/ml (n = 26)	VL > 400 copies/ml (n = 77)	All Patients (n = 103)	*P*[a]
Age (median [range]) (y)	7 (2–14)	10 (1–17)	9 (1–17)	.08
Age groups (n [%])				
≤59 mo	4 (15)	14 (18)	18 (17)	.77
5–12 y	18 (69)	46 (60)	64 (62)	
13–18 y	4 (15)	17 (22)	21 (20)	
Sex, male (n [%])	15 (58)	38 (49)	53 (51)	
Regimen (n [%])				.60
ZDV, 3TC, EFV	0 (0)	1 (1)	1 (1)	
ZDV, 3TC, NVP	2 (8)	10 (13)	12 (12)	
D4T, 3TC, EFV	10 (38)	19 (25)	29 (28)	
D4T, 3TC, NVP	14 (54)	47 (61)	61 (59)	
ART duration (median [range]) (mo)	22 (6–31)	13 (6–29)	14 (6–31)	.02
WHO stage (n [%])				
I	1 (4)	10 (13)	11 (11)	.10
II	9 (35)	23 (30)	32 (31)	
III	16 (62)	34 (44)	50 (49)	
IV	0 (0)	10 (13)	10 (10)	
CD4 count (median [range]) (cells/μl)	693 (98–2569)	168 (4–1953)	238 (4–2569)	<.001
CD4 count group (n [%])				
<200 cells/μl	3 (12)	46 (60)	49 (48)	<.001
200–350 cells/μl	1 (4)	10 (13)	11 (11)	
>350 cells/μl	22 (85)	21 (27)	43 (42)	
CD4% (median [range])	28 (7–47)	9 (0–33)	12 (0–47)	<.001
CD4% group (n [%])				
<15%	2 (8)	54 (70)	56 (54)	<.001
15%–25%	8 (31)	17 (22)	25 (24)	
>25%	16 (62)	6 (8)	22 (21)	
Viral load (median [range]) (copies/ml)	—	37 080 (627–750 000)	—	—

Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; D4T, stavudine; EFV, efavirenz; NVP, nevirapine; VL, viral load; WHO, World Health Organization; ZDV, zidovudine.
[a] *P* values are from Wilcoxon rank-sum tests for continuous variables or Fisher exact tests for categorical/ordinal variables.

misclassification with virologic failure. This discordance may result from higher failure rates in children, the selected CD4 thresholds, or selection bias. The results of this study provide further evidence to support the 2013 guidelines, which recommend routine VL-based monitoring given the poor accuracy of immunologic monitoring guidelines. This should further motivate treatment programs to strategically plan for such monitoring despite the associated financial and programmatic constraints.

In our data set, there were few VL tests performed in the 0- to 2-year age group, which is likely reflective of the lack of infants started on ART early in life. The 2013 consolidated WHO treatment guidelines recommend ART initiation for all children <5 years old and increase eligibility for children ≥5 years old [2]. Given the increase in the number of children starting ART and the high risk of virologic failure in this age group, it is particularly important to evaluate infants and young children in future studies.

Our study was limited by the nature of patient selection. Clinicians tested VLs in patients suspected of experiencing immunologic/clinical treatment failure. In addition to this being a subjective measurement, patients not suspected of experiencing treatment failure would not have undergone VL testing and, therefore, would not have been included. Therefore, these data may not be generalizable to all HIV-infected children on ART, and more comprehensive studies are essential. In addition, confirmatory CD4 and VL testing was not available, and although this represents a limitation, it reflects reality in RLS. The fact that only 2 children classified as having experienced virologic failure had a VL between 400 and 1000 copies/ml supports the low likelihood that the effect was due to virologic blip. Regardless, this study adds to the current pediatric literature and comprises a true cohort of those patients who most urgently require assessment for virologic failure.

In summary, the data presented here augment the evidence supporting the need to develop better monitoring algorithms for HIV-infected patients on ART in RLS with no or limited VL testing. In such settings, the usage of currently available guidelines may lead to unacceptably high rates of treatment failure misclassification. Consequences, such as inappropriate treatment changes to second-line ART or accumulation of resistance, must be minimized and highlight the need for clinicians to be aware of the limitations of the guidelines, not only in adults but also in children on ART. The limited pediatric literature on the

topic and pediatric-specific issues, such as limited drug formulations and dosing and adherence concerns, further emphasize this need. Affordable and available VL assays for ART monitoring for children in RLS are urgently needed to ensure optimal treatment outcomes for HIV-infected children.

Supplementary Data

Supplementary materials are available at Journal of *the Pediatric Infectious Diseases Society* online.

Notes

Acknowledgments. We thank Dr. Sylvester Kimaiyo, Dr. E. Jane Carter, Dr. Joseph Mamlin, Dr. Robert Einterz, Dr. Timothy Flanigan, Dr. Joseph I. Harwell, Dr. Michael Waxman, Prof Ayaya, Dr. Tenge, Dr. Nabakwe, Dr. Gisore, Dr. Chumba, Dr. Marete, Victor Cheboi, Jane Chemwon, Irene Tugoi, Mabonga, Lucy Warui, Mary Rugut, and other staff at AMPATH, the Moi Teaching and Referral Hospital, and Moi University School of Medicine for their support of this study.

Financial support. This work was supported in part by the President's Emergency Plan for AIDS Relief (PEPFAR) through the US Agency for International Development (USAID) under the terms of Cooperative Agreement AID-623-A-12-0001. It is made possible through joint support of the USAID. The contents of this publication are the sole responsibility of the authors and do not necessarily reflect the views of the USAID or the US government. Drs. Kantor, Hogan, and Dufort and Ms. DeLong were supported by the infrastructure and resources provided by the Lifespan/Tufts/Brown Center for AIDS Research, a National Institutes of Health (NIH)-funded program (P30AI42853). Ms. Mann was supported by NIH grant T32DA13911.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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