Improving Methods to Classify Perinatal versus Nonperinatal HIV Acquisition in Young Adolescents 10–14 Years of Age

Priscilla Ruvimbo Tsondai, MD, MPH, Mary-Ann Davies, MD, PhD,* Thida Singtoroj, PhD,† Nicola Maxwell,* Catherine C. McGowan, MD,‡ Wipaporn N. Songtaweesin, MBBS,§ Karl-Günter Technau, PhD,¶ Azar Kariminia, PhD,‖ Cleophas Chimbetete, MD, PhD,** Regina C. M. Succi, MD, PhD,†† Jorge Pinto, MD, DSc,‡‡ Vanessa Rouzier, MD,§§ Marco Tulio Luque, MD,¶¶ and Annette H. Sohn, MD,† for the IeDEA Consortium*

Abstract: Mode of HIV acquisition for adolescents with HIV is often not recorded within routine healthcare databases. Hence, age at enrollment in HIV care is often used as a proxy for perinatal versus nonperinatal infection. Using routine cohort data from adolescents presenting for HIV care 10–14 years of age, we developed logistic regression models to predict likely mode of infection.

Key Words: adolescents, HIV, mode of infection, area under the receiver operating characteristic curve

(*Pediatr Infect Dis J* 2021;40:453–456)

The population of adolescents living with HIV (ALH) is comprised those who acquired HIV perinatally and those who were infected nonperinatally. While similar in some ways, adolescents living with perinatally acquired HIV (ALPH) have differing sociodemographic and disease characteristics, vulnerabilities and risk behaviors when compared with those with more recent infection. ALPH have longstanding HIV infection, and those presenting for HIV care for the first time during adolescence would have lived with untreated HIV for prolonged periods.[1]

While most children with perinatally acquired HIV are expected to have presented for the first time for HIV care as infants or children, up to a third may have slow-progressing infection and could survive into adolescence without treatment.[2] The Spectrum AIDS Impact Model has estimated median survival for children infected with HIV after the first year of life of up to 14 years in the absence of any antiretroviral treatment.[3,4] This means, for adolescents presenting for the first time for HIV care between the ages of 10 and 14 years, perinatal and nonperinatal HIV acquisition are both plausible. In resource-limited settings, however, the mode of infection of children and ALH is frequently not ascertained or captured within routine healthcare databases. In an effort to distinguish these 2 subgroups within data, a number of analyses have used age cutoffs at enrollment as a proxy to categorize the likely mode of HIV acquisition, with those entering HIV care at specific ages, such as <10[5,6] or <15 years,[7] assumed to have perinatally acquired HIV. The optimal age threshold to use in such situations is unclear and using age cutoffs alone could result in substantial misclassification.

Using data from the International epidemiology Databases to Evaluate AIDS (IeDEA) Southern Africa (IeDEA-SA), IeDEA Asia-Pacific (IeDEA-AP) and The Caribbean, Central and South America network for HIV epidemiology (CCASAnet) cohorts, we aimed to determine characteristics of ALH 10–14 years of age at enrollment into routine HIV care that could predict likely mode of infection and be used to better distinguish likely mode of infection.

METHODS

We conducted an analysis on prospectively collected data of ALH who enrolled into HIV care 10–14 years of age within the IeDEA-SA, IeDEA-AP and CCASAnet cohorts, from 1990 to 2017. IeDEA is an international research consortium of seven regional collaborations of HIV observational databases (www.iedea.org). Each regional collaboration combines routine observational data from HIV care and treatment programs from several countries in their respective regions (www.iedea.org/regions). Characteristics and outcomes of ALH across the IeDEA collaboration have been described elsewhere.[7–9]

Ethics

All IeDEA participating sites have local ethics approval from their local Institutional Review Boards (IRB) to contribute

Accepted for publication December 19, 2020

From the *Centre for Infectious Disease Epidemiology and Research, School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa; †TREAT Asia/amfAR, The Foundation for AIDS Research, Bangkok, Thailand; ‡Vanderbilt University Medical Center, Nashville, Tennessee; §Center of Excellence for Pediatric Infectious Diseases and Vaccines, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; ¶Empilweni Services and Research Unit, Department of Paediatrics & Child Health, Rahima Moosa Mother and Child Hospital, Faculty of Health Sciences, University of the Witwatersrand, South Africa; ‖The Kirby Institute, UNSW Sydney, Australia; **Newlands Clinic, Harare, Zimbabwe; ††Escola Paulista de Medicina, Pediatrics Department, Universidade Federal de Sao Paulo, Sao Paulo, Brazil; ‡‡Universidade Federal de Minas Gerais, Belo Horizonte; §§Les Centres GHESKIO, Port-au-Prince, Haiti; and ¶¶Instituto Hondureño de Seguridad Social and Hospital Escuela Universitario, Tegucigalpa, Honduras.

The International Epidemiology Databases to Evaluate AIDS (IeDEA) was supported by the US National Institutes of Health's National Institute of Allergy and Infectious Diseases and, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development: Asia-Pacific (U01AI069907); CCASAnet (U01AI069923); Southern Africa (U01AI069924). This work was also funded by the US National Institutes of Health's National Institute of Allergy and Infectious Diseases for GRADUATE (R21HD089859). This work is solely the responsibility of the authors and does not necessarily represent the official views of any of the institutions mentioned above. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

A.H.S. has received grant funding to her institution from ViiV Healthcare. The other authors have no conflicts of interest to disclose.

M.-A.D. conceived and designed the study. C.C.M., W.N.S., K.-G.T. and C.C. collected the data. N.M. and T.S. contributed to the implementation of the research. P.R.T. performed the analysis and drafted the manuscript. M.-A.D. and A.H.S. supervised the findings of this work. All authors commented on the manuscript and have read and approved the final manuscript.

Address for correspondence: Priscilla Ruvimbo Tsondai, MPH, MD, School of Public Health and Family Medicine, University of Cape Town, Observatory, Cape Town 7925, South Africa. E-mail: priscilla.tsondai@uct.ac.za.

ISSN: 0891-3668/21/4005-0453
DOI: 10.1097/INF.0000000000003059

de-identified, anonymized, individual patient data to their IeDEA regional data centers. Each data center has its own IRB approval to receive, combine and analyze this data. Patients/caregivers either provided informed consent for inclusion of their data in the respective regional databases or regional IRBs have granted consent waivers.

Measurements and Outcomes

Characteristics of adolescents presenting for HIV care 10–14 years of age included demographic, anthropometric and recorded mode of infection. Recorded mode of infection was categorized as perinatal, nonperinatal and unknown. Perinatally acquired HIV was as reported by the sites, and included acquisition of HIV during pregnancy, labor and delivery or postnatally through breast-feeding. All other means of HIV acquisition were included as nonperinatally acquired HIV. Height measures were converted to age and sex-specific height-for-age z-scores (HAZ) using the "who2007" Stata macro.[10]

The main outcome of interest was the mode of HIV acquisition, categorized as perinatal and nonperinatal.

Statistical Analysis

Characteristics of ALH enrolling into HIV care 10–14 years of age were described by mode of HIV infection (perinatal vs. nonperinatal vs. unknown) using medians with interquartile ranges (IQRs) and frequency distributions. To describe characteristics at entry into care, measurements from the date closest to the date of entry into care up to 6 months after were used. Using patient characteristics of adolescents with a documented mode of infection, logistic regression models to predict the likely mode of infection were developed. The predictive ability of the different models generated was compared using sensitivity, specificity and area under the receiver operating characteristic curve (AUROC). As our model was aimed at prediction, variable and model selection was based on goodness-of-fit statistics. The different predictive models were then used to classify the mode of HIV infection in those with an undocumented mode of infection and the classification results from models with different combinations of patient characteristics (age alone vs. age with HAZ and sex vs. age with HAZ, sex and CD4 count) compared.

Statistical analyses were done using Stata 15.0 (StataCorp, College Station, TX).

RESULTS

We included 10,349 adolescents (54% female) from 16 countries (9402 from IeDEA-SA, 718 from IeDEA-AP, 229 from CCASAnet). About two-thirds (65%) were <13 years of age at entry into HIV care (median [IQR] age 12.2 years [11.1; 13.5]). The mode of HIV infection was documented in 20% (n = 2076); among these, 2000 (96%) acquired HIV perinatally (53% female), and 76 (4%) acquired HIV nonperinatally (45% female). Adolescents with perinatal HIV, when compared with those with documented nonperinatal HIV, were more likely to be female (53% vs. 45%), slightly younger (median age 11.8 [10.8; 13.0] vs. 12.7 [11.7; 14.2] years), and had lower HAZ (median HAZ −2.27 [−3.10; −1.46] vs. −1.60 [−2.58; −0.82]) at enrollment into HIV care. There were no differences observed with regards to the median CD4 count at entry into care (186 [55; 415] vs. 190 [54; 431] cells/μL).

In multivariable logistic regression models using characteristics of adolescents with a documented mode of infection, perinatal HIV acquisition was associated with younger age at presentation (adjusted odds ratio [aOR] for each increasing year 0.62, 95% confidence interval [CI] 0.52; 0.75), lower HAZ (aOR for a 1 unit increase 0.65, 95% CI 0.53; 0.79), and being female (aOR 1.64, 95% CI 0.99; 2.72). CD4 count at the first presentation was not predictive of perinatal HIV acquisition.

When considering only one predictive variable using models of characteristics of adolescents with documented mode of infection, a model with age alone (AUROC 0.6572, 95% CI 0.5903; 0.7241) had the highest predictive ability when compared with models with only HAZ (AUROC 0.6257, 95% CI 0.5568; 0.6946), sex (AUROC 0.5436, 95% CI 0.4863; 0.6009) or CD4 count (AUROC 0.5248, 95% CI 0.4427; 0.6070) (Fig. 1). The model including age and HAZ had a higher AUROC (0.7085; 95% CI 0.6420; 0.7749), with a further increase in predictive ability after adding sex (0.7208; 95% CI 0.6577; 0.7839) and CD4 count (0.7383; 95% CI 0.6635; 0.81304) (Fig. 1).

When using a model based on age alone, 75% (95% CI 74; 76) of adolescents 10–14 years of age with unknown mode of infection were classified as having perinatally acquired HIV. This proportion decreased to 65% (95% CI 64; 66) with the addition of HAZ and sex to the model. However, these additions increased the proportion that could not be classified due to missing HAZ data (14%, 95% CI 13%; 15%). Further addition of CD4 count to the model decreased the proportion classified as perinatally infected to 35% (95% CI 34; 36) and increased the proportion that could not be classified to 56% (95% CI 55%; 57%).

DISCUSSION

Among ALH presenting for HIV care 10–14 years of age, only <20% of adolescents had documented mode of infection, highlighting the need for predictive models to address this data gap. Among those with a recorded mode of infection, <5% were reported as having acquired HIV nonperinatally, suggesting that the majority had acquired HIV perinatally. An age threshold of <10 years at enrollment as a proxy for perinatal infection in this population would thus have misclassified 97% of these adolescents. Raising the threshold to 15 from 10 recognizes the younger adolescents presenting very late for care, with severely suppressed immune systems and stunting. These adolescents are often a neglected group which may not fit in with pediatric clinics but also might not fit with older adolescent clinics where most patients have nonperinatally acquired HIV.

Predictive models of mode of HIV acquisition based on age, sex and HAZ had a much higher AUROC than a model using age alone and misclassified considerably fewer adolescents compared with using an arbitrary age threshold of <10 years as a proxy for likely perinatally acquired HIV. Importantly, in our routinely collected data, the mode of HIV acquisition could be classified in 86% of adolescents using age, sex and HAZ. This information provides a basis on which to test additional variables and build a more reliable algorithm.

Our study is limited by a relatively small proportion of adolescents having a documented mode of infection and limited additional predictor variables (eg, no data on parental death). There is also a risk of misclassification for those incorrectly reported as not having perinatally acquired HIV due to the lack of parental HIV information. Nonetheless, predictive models based on a small number of variables that are routinely available may be useful for analysts wanting to include likely mode of HIV acquisition when the mode of HIV acquisition is not recorded. If age alone is used as a proxy for mode of HIV acquisition due to missing data on predictor variables, careful consideration should be given to the appropriate age threshold for assuming likely perinatally acquired HIV in different contexts.

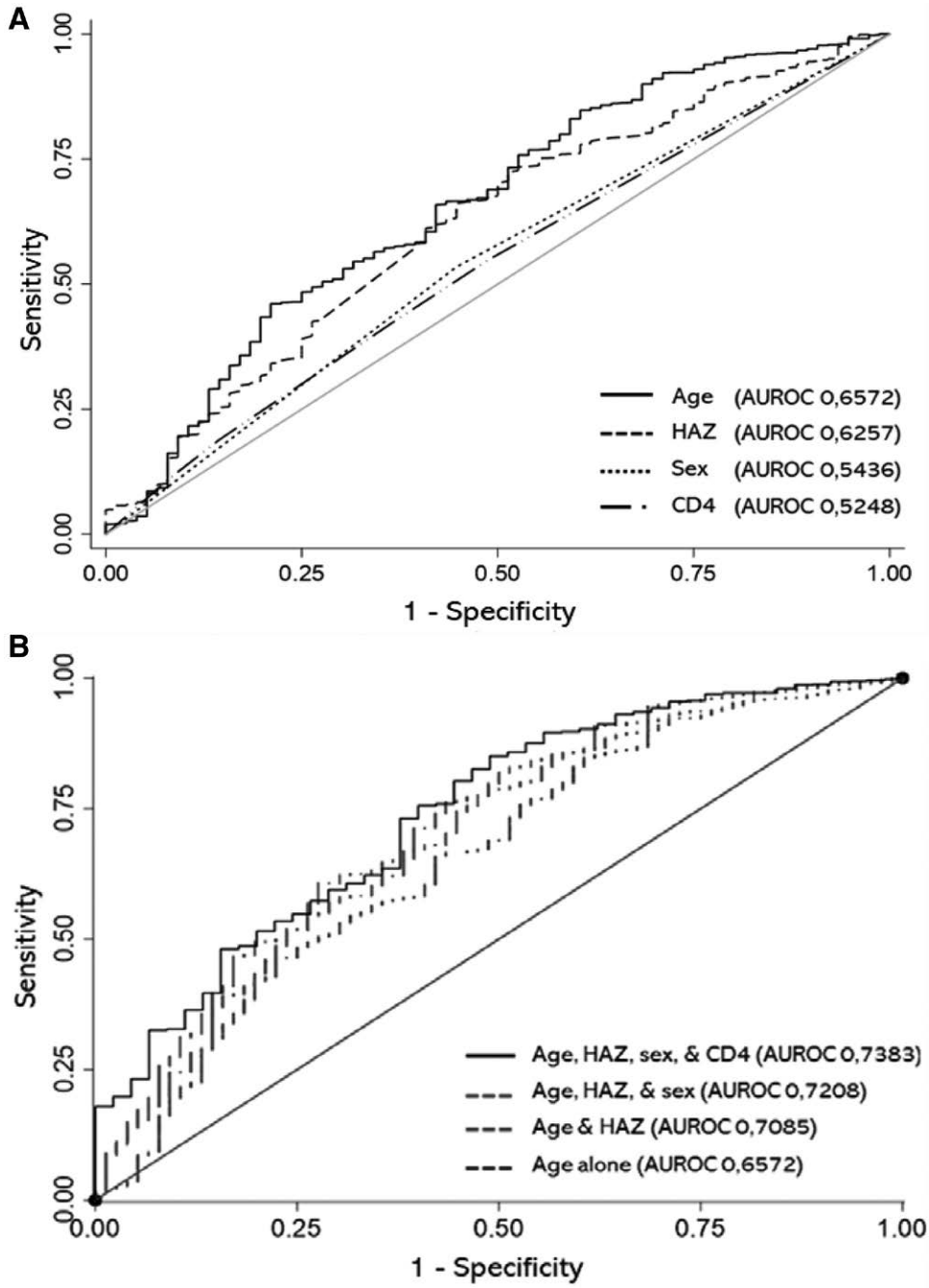

FIGURE 1. Areas under the ROC for (A) models with individual covariates and (B) models with different covariates for predicting perinatal HIV acquisition among ALH presenting for HIV care 10–14 years of age.

ACKNOWLEDGMENTS

We thank the adolescents whose data were used in this analysis, as well as their caregivers. We also thank all staff at participating sites for providing patient care and preparation of data contributed to the IeDEA consortium. Lastly, we thank the IeDEA-SA, IeDEA-AP and CCASAnet Data Centre teams.

Regional acknowledgements of site investigators, cohorts, study teams and administrators, data managers, and coordinating and data centers are available at: https://www.iedea.org/resources/.

REFERENCES

1. Sohn AH, Hazra R. The changing epidemiology of the global paediatric HIV epidemic: keeping track of perinatally HIV-infected adolescents. *J Int AIDS Soc.* 2013;16:18555.
2. Bernays S, Jarrett P, Kranzer K, et al. Children growing up with HIV infection: the responsibility of success. *Lancet.* 2014;383:1355–1357.
3. Marston M, Becquet R, Zaba B, et al. Net survival of perinatally and postnatally HIV-infected children: a pooled analysis of individual data from sub-Saharan Africa. *Int J Epidemiol.* 2011;40:385–396.
4. Mahy M, Penazzato M, Ciaranello A, et al. Improving estimates of children living with HIV from the spectrum AIDS impact model. *AIDS.* 2017;31(suppl 1):S13–S22.

5. Jesson J, Schomaker M, Malasteste K, et al; IeDEA global cohort consortium. Stunting and growth velocity of adolescents with perinatally acquired HIV: differential evolution for males and females. A multiregional analysis from the IeDEA global paediatric collaboration. *J Int AIDS Soc.* 2019;22:e25412.
6. Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) Global Cohort Collaboration. The epidemiology of adolescents living with perinatally acquired HIV: a cross-region global cohort analysis. *PLoS Med*. 2018;15:e1002514.
7. Kariminia A, Law M, Davies MA, et al; IeDEA. Mortality and losses to follow-up among adolescents living with HIV in the IeDEA global cohort collaboration. *J Int AIDS Soc.* 2018;21:e25215.
8. Desmonde S, Neilan AM, Musick B, et al; IeDEA. Time-varying age- and CD4-stratified rates of mortality and WHO stage 3 and stage 4 events in children, adolescents and youth 0 to 24 years living with perinatally acquired HIV, before and after antiretroviral therapy initiation in the paediatric IeDEA Global Cohort Consortium. *J Int AIDS Soc.* 2020;23:e25617.
9. Wools-Kaloustian K, Marete I, Ayaya S, et al. Time to first-line ART failure and time to second-line ART switch in the IeDEA pediatric cohort. *J Acquir Immune Defic Syndr.* 2018;78:221–230.
10. World Health Organization. WHO Child Growth Standards. STATA WHO 2007 package [WHO web site]. Available at: http://www.who.int/entity/growthref/tools/who2007_stata.zip. Accessed February 1, 2020.