Longitudinally Evaluating the Lung Function of Children in Low- and Middle-income Countries: It's About Time

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(See the Major Article by Githinji et al on pages 483–90.)

Approximately 90% of the estimated 180 000 new pediatric human immunodeficiency virus (HIV) infections in 2017 occurred in sub-Saharan Africa [1]. Although access to life-saving antiretroviral therapy (ART) for HIV-infected African children remains unsatisfactorily low, mortality among children perinatally infected with HIV has declined over the past decade [2]. As a result, increasing numbers of HIV-infected children in sub-Saharan Africa are surviving into adolescence [3]. It has been well documented that a high prevalence of perinatally infected adolescents in sub-Saharan Africa have chronic respiratory disease and lung function impairment [4, 5], yet we currently lack a more granular understanding of how this impairment may change over time, especially in the presence of ART.

In *Clinical Infectious Diseases*, Githinji and colleagues adeptly address this evidence gap. The authors report on the longitudinal lung function of 515 perinatally HIV-infected adolescents over a 2-year period who received ART in Cape Town, South Africa [6]. In their study, the authors matched an HIV-uninfected comparator group of 110 adolescents without known chronic lung disease to HIV-infected cases

on age, sex, and ethnicity. Using a validated commercial device, the investigators conducted spirometry with and without bronchodilators according to international guidelines [7]. Spirometry results were interpreted using the 2012 Global Lung Function Initiative (GLI-2012) reference values derived from African Americans [8]. The authors used 2 sample *t* tests to compare lung function at baseline and 2 years with models adjusted for demographic and clinical covariates and mixed-effects modeling to compare longitudinal changes and lung function determinants.

The main findings from this longitudinal study are important. Consistent with prior publications, Githinji et al found that adolescents perinatally infected with HIV had lower lung function compared to reference values and HIV-uninfected adolescents. However, this study's novel longitudinal data show that among this population of HIV-infected adolescents, the key lung function parameters of forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV₁) largely tracked along similar, albeit lower, trajectories as those of HIV-uninfected adolescents. These results suggest that in most HIV-infected children ART cannot only preserve lung function but also reestablish a normal trajectory of lung growth and development despite earlier lung injury. However, longer follow-up is needed, as the investigators also reported near doubling of the prevalence of airway obstruction, primarily due to increases in fixed, irreversible obstruction. This progression of lung disease may be

due to either prior insults or ongoing subclinical lung injury from a myriad of possible causes, resulting in spirometry patterns consistent with bronchiolitis obliterans. These observations raise concern that lung function trajectories may plateau earlier than would be otherwise expected in this cohort, leaving many of these children even more susceptible to adverse outcomes from infectious or environmental pulmonary insults than their uninfected counterparts. Chronic lung disease progression may contribute to the rising mortality rates among older perinatally HIV-infected adolescents and deserves further exploration [3].

The authors also found that, regardless of HIV status, a prior history of pulmonary tuberculosis or severe lower respiratory tract infection were each associated with lower lung function for an adolescent, suggesting that early insults may track through life. This implies that investments toward prevention and/or early identification and treatment of lower respiratory tract infections must continue to be strengthened throughout sub-Saharan Africa and other regions. For instance, while the introduction of the pneumococcal conjugate vaccine continues to progress globally, the momentum must be sustained as more countries transition away from Gavi funding [9]. New vaccines that target key respiratory viruses such as the respiratory syncytial virus are on the horizon and, if efficacious, present an exciting opportunity to potentially further optimize lung health [10]. The results from Githinji et al provide indirect evidence that evaluations of new

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vaccines against lung function endpoints are needed considering such data are likely to provide a more comprehensive picture of the long-term lung health impact of these vaccines.

This study population may not be generalizable to all sub-Saharan African perinatally HIV-infected adolescents. Although this is a perinatally infected adolescent cohort, the median age at ART initiation exceeded 4 years. Given current guidelines that recommend ART initiation at first diagnosis, these results reflect later identification of HIV and initiation of ART. These data may therefore underestimate the potential benefit of ART in maintaining lung function when initiated earlier in life. On the other hand, since this population of children is likely representative of the slow-progressor HIV phenotype, the data may also be interpreted as potentially overestimating the lung function of other perinatally infected adolescents who are not slow progressors. Additional studies on cohorts of mixed slow- and fast-progressor adolescents diagnosed and initiated on ART earlier in life will be important next steps to gain a more balanced understanding of the lung health impact of ART. Studying cohorts characterized by earlier ART initiation also presents an opportunity to more closely estimate the in utero effects of HIV on fetal lung development, along with an understanding of the developmental plasticity of the lungs in the presence of HIV and ART at younger ages.

Two limitations of this analysis require further discussion. First, the authors relied on spirometry to make inferences about the presence of restrictive and mixed obstructive–restrictive lung function abnormalities. In order to be definitive, such abnormalities require diagnostic confirmation by determining the total lung capacity (TLC), which is traditionally measured through costlier and technically challenging approaches such as body plethysmography, gas washout, or dilution techniques [11]. Among white adults, for example, spirometry measurements of FVC are associated with a low TLC in just half of patients [12, 13]. The authors’

conclusions around restrictive and mixed lung function physiology should be contemplated with this limitation in mind. Future studies would benefit from more definitive lung volume evaluation.

Second, normative lung function prediction equations are based on Western populations due to a paucity of data from other regions such as sub-Saharan Africa. As a result, in this study the authors used GLI-2012 reference values from African Americans that have been reported as valid for use in healthy, well-nourished sub-Saharan African children [14]. To foster generalizability of results across studies, the GLI-2012 reference values are also recommended by international bodies for use in research [15]. Nevertheless, it remains unclear whether these values are appropriate for malnourished African children with smaller chest dimensions and lung volumes [14]. The interpretation of spirometry measures reported in this study may therefore be systematically low due to the presence of malnourished children in this cohort and may, to some degree, reflect smaller lung volumes rather than solely impaired lung function. Although the authors do not present data on the percentage of children who are malnourished, the proportionally low estimates of FVC and FEV₁ z scores among both HIV-infected and HIV-uninfected adolescents in the article’s Table 2 suggest that such a low lung volume spirometry pattern, rather than only impairment, may be present. Whether or not these findings are due to restrictive lung disease, small lung volumes, or a combination thereof can only be resolved by establishing lung function reference values specific to sub-Saharan African children and conducting more definitive lung volume measurements.

This laudable study of longitudinal lung function among perinatally HIV-infected adolescents is long overdue. The authors have provided an important contribution to the literature and our understanding of how the lungs of HIV-infected adolescents may continue to grow and develop in the face of ART. Githinji et al’s work has raised provocative questions and

should serve as a solid platform for future pediatric lung health research in low- and middle-income countries, both within the HIV continuum and beyond.

Note

Potential conflicts of interest. The author has no potential conflicts of interest to disclose. The author: No reported conflicts of interest. The author has 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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