Original Article

Small-airway disease and its reversibility in human immunodeficiency virus-infected children on highly active antiretroviral therapy: A cross-sectional study in an African setting

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Abstract:

BACKGROUND: Lung function abnormalities may occur in children with human immunodeficiency virus (HIV) infection. Small-airway disease (SAD) precedes abnormalities in forced expiratory volume in 1 s (FEV_1).

OBJECTIVE: This study aims to assess the presence and reversibility of SAD in HIV-infected children using the Global Lung Function Initiative standards.

METHODS: A cross-sectional study was conducted over 6 months at the Paediatric HIV Clinic of the University of Nigeria Teaching Hospital in Enugu, Southeast Nigeria. Eligible consenting children with HIV infection were recruited. Lung function was measured, and the reversibility of FEV_1 and forced vital capacity (FVC) was assessed at 12% while that of forced expiratory flow between 25% and 75% (FEF_{25-75}) was assessed at 12%, 15%, and 20%. Predictors of abnormal Z-score values were determined by multivariate linear and logistic regressions. Statistically significant values were set at $P < 0.05$.

RESULTS: The mean Z-score for FEV_1, FVC, and FEF_{25-75} was – 2.19, –1.86, and – 1.60, respectively. Most patients (73%) had abnormal FEV_1, while 52% had abnormal FEF_{25-75}. Significant changes in FEV_1 ($P = 0.001$) and FEF_{25-75} ($P < 0.001$) occurred after the bronchodilator response (BDR) test. Of the children whose FEV_1 showed positive BDR, 70.9% had low $zFEV_1$; 50% had low $zFEF_{25-75}$, while all had low FEV_1. Nutritional status (Z-score for body mass index) was significantly associated with low FEV_1.

CONCLUSIONS: Abnormal FEF_{25-75} as a marker of SAD and FEV_1 with a positive BDR are common in HIV-infected children. These lung function abnormalities justify long-term follow-up for these patients.

Keywords:

Africa, children, human immunodeficiency virus, Nigeria, small-airway disease, spirometry

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Human immunodeficiency virus (HIV) infection in children remains a global health challenge.[1-3] Fortunately, highly active antiretroviral therapy (HAART) has significantly reduced morbidity and mortality among infected children.[3] Despite prolonged patient survival and the favorable outcome from eliminating the frequent chest infections,[4,5] HIV still causes airway hyper-responsiveness and obstruction over time.[6] The pathophysiologic trajectory involves a rapid progression to asthma and

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chronic obstructive pulmonary disease later in adult life.[4,6]

Forced expiratory volume in 1 s (FEV_1) mainly reflects obstruction in the larger airways.[6] However, a significant degree of small-airway disease (SAD) precedes abnormalities in FEV_1.[6] Examination of the mid-portion of expiratory flow may, therefore, offer more information on small-airway pathology. The forced expiratory flow between 25% and 75% (FEF_{25-75}) of the forced vital capacity (FVC) is one of the most commonly used parameters of small-airway pathology.[6-9] Besides its inaccuracy in assessing SAD, the lung clearance index is usually limited to research laboratories due to cost, expertise, and availability.[6] Low FEF_{25-75} is a sensitive marker for airway obstruction in asymptomatic asthmatics[10] and a known marker of methacholine responsiveness in symptomatic asthmatic children.[11] It also predicts bronchodilator response (BDR) to albuterol.[9]

Spirometry has been used to evaluate HIV-related lung changes in children, and abnormalities in FEV_1, FVC, and low FEV/FVC have been reported.[12-14] Furthermore, other authors reported positive BDR in HIV-infected children.[13-15] It is postulated that if SAD exists in these children, surrogate parameters such as FEV_1 and the additional use of FEF_{25-75} could help to identify them on time. The present study thus focuses on detecting lung function abnormalities in HIV-infected children, with emphasis on FEF_{25-75} as an early marker of SAD. Using the more robust Global Lung Function Initiative (GLI) standards,[16] we aimed to assess the presence and reversibility of SAD in HIV-infected children. The possible risk factors for their lung function abnormalities were also evaluated.

Methods

Study site, participants' selection, and procedures

Ethical approval was obtained from the Health Research and Ethics Committee (HREC) of the University of Nigeria Teaching Hospital, Ituku-Ozalla, Enugu, before commencing the study (Approval number: HREC/05/01/2008B). The study was cross sectional and was conducted over 6 months (from March to September 2019) at the Pediatric HIV Clinic of the hospital. Eligible individuals were previously diagnosed HIV-infected children, already registered and attending the Pediatric HIV Clinic, and children who gave assent or had informed written consent signed by their caregivers. Data were collected with interviewer-administered questionnaires and extraction of data from medical records. Extracted information from participants included age, gender, current and previous health status, and the HAART medications they were receiving. HAART was defined as the use of at least three medications from two classes of antiretroviral drugs within the previous 3 months as determined from information obtained from each patient's filed records. Socioeconomic class (SEC) was determined by standard methods using parental level of education and type of vocation, and these were categorized into lower Class 3 (SEC 4 and 5), middle Class 2 (SEC 2 and 3), and upper Class 1 (SEC 1).[17] Children who had physician-diagnosed or self-reported asthma or had been on any bronchodilator medications or had a new or increasing cough, shortness of breath, or fever in the past 4 weeks or were severely ill or could not meet the American Thoracic Society (ATS) requirement for acceptable and reproducible spirometry[18] were excluded. The weight and standing height of each participant were measured, and subsequently, the height-for-age Z-score and body mass index (BMI) were calculated. The spirometry procedure was explained and demonstrated with the ATS/European Respiratory Society (ERS) guidelines.[18] We used ATS-certified handheld ndd EasyOne™ spirometers, portable and battery operated. The spirometers were calibrated before and after each measurement sessions using a certified 3 L syringe. Each child was given the opportunity to make a maximum of 8 attempts, and 3 acceptable and repeatable maneuvers were selected. Any participant who failed to meet these criteria was further excluded from the study. This was done till the sample size was consecutively reached. Flow–volume curves were also manually inspected to ensure that acceptability criteria were met. After the successful prebronchodilator blow, each participant then received 400 μg of salbutamol from a pressurized metered-dose inhaler (pMDI) device in four separate doses of 100 μg through a spacer, and spirometry was repeated after 15 min.[18-20] The value used for cut-off decision point in deciding abnormality in Bronchodilator response (BDR) for FEV1 and FVC was done using 12% change from baseline while that for FEF_{25-75} was done using all 3:12%, 15%, and 20% change from baseline.

The pre- and post-BDR values of FEV_1, FVC, FEV_1/FVC ratio, and FEF_{25-75} for each participant were obtained and expressed as Z-scores. The participants were subsequently reviewed according to the HIV clinic protocol. Those with abnormal lung function patterns were counseled appropriately and given appointments for future follow-up in the children's respiratory clinic.

Sample size and statistical analysis

Using the standard deviation (SD) of FVC in a cohort of HIV-infected children for sample size calculation,[12] a minimum sample size of 90 participants was required. The Shapiro–Wilk test was used to test for normality for continuous variables. The records of the absolute values were first stored within the spirometer and all identifiers anonymized. They were then exported to the GLI reference equations software where they were adjusted for standing height, age, sex, and ethnicity to obtain the corresponding Z-scores, predicted values,

and the lower limit of normal (LLN) values (defined as 1.64 SD below the mean and describes the lowest fifth centile).[15] These values provided the cutoff for determining abnormal airflow. Positive reversibility to bronchodilators was ascertained using the accepted consensus of ERS/ATS, which accepts BDR as positive when FEV_1 increases to >12%.[18-20] A positive change of up to 20% was applied to increase the specificity and sensitivity of FEF_{25-75}-related BDR response, given several disadvantages of relying on FEF_{25-75}.[21]

The proportion of participants with airway obstruction as determined by both lung function values below the 5% lower limit of normal adjusted for age and FEV/FVC less than 0.80 were calculated. Thus the disease abnormality classification for the spirometry patterns obtained were: 'normal' if the FEV1 and FVC values were simultaneously ≥LLN; and categorized as 'obstructive' if the FEV/FVC was either < LLN or less than 80% of absolute percentage value; and as 'restrictive pattern', 'fixed airway obstruction' or 'mixed' if the FVC is <LLN or both the FEV1/FVC and FVC are <LLN. The paired *t*-test for the pre- and post-BDR mean scores and Chi-square tests for categorical variables were calculated. Univariate analyses were performed to determine variables associated with FEV_1 and FEV1/FVC. We used multivariate linear and logistic regressions to determine the predictors of abnormal Z-score values of the spirometric lung function parameters. Significant findings were represented in tables and figures. Statistically significant values were set at $P < 0.05$.

Results

Characteristics of study participants

Of the eligible 104 participants (out of a total of 137 that performed spirometry), the mean age was 13.96 ± 3.23 years, with 56/104 (53.8%) males [Table 1]. There were no self-reported active smokers or exposure to environmental tobacco smoke. There was no reported personal or family history of asthma in the eligible group, and none of the participants was on treatment for tuberculosis or any other chronic respiratory disease. A total of 67/104 (64.4%) participants resided in rural or semi-urban settings, and the social status showed that 25/104 (24.0%) and 39/104 (37.5%), respectively, belonged to the middle SEC 3 and lower SEC 4. Seventy-seven participants (74.0%) were still on first-line HAART, while 27/104 (26.0%) received an alternative to mainstream first-line HAART, such as dolutegravir or the second-line HAART [Table 1].

Table 1: Descriptive characteristics of study participants (*n*=104)

Variables	Outcome/Proportion (*N*=104)
Mean age in years±SD	13.96±3.23
zBMI±SD	−0.81±1.18
zHeight±SD	−0.52±1.65
Gender, *n* (%)	
Male	56 (53.8)
Female	48 (46.2)
SEC, *n* (%)	
Class 1	10 (9.6)
Class 2	15 (14.4)
Class 3	25 (24.0)
Class 4	39 (37.5)
Class 5	15 (14.4)
HAART type	
On traditional first-line HAART, *n* (%)	77 (74.0)
On alternative/second line HAART, *n* (%)	27 (26.0)

zBMI=Z-score for body mass index, SD=Standard deviation, SEC=Socioeconomic class, HAART=Highly active antiretroviral therapy

Lung function outcome in children with human immunodeficiency virus

For all participants, the prebronchodilator mean Z-score for FEV_1, FVC, and FEF_{25-75} was −2.19, −1.86, and −1.60, respectively [Table 2]. The significant changes after BDR were noted for the FEV1 ($P = 0.001$) and FEF_{25-75} ($P < 0.001$) [Table 3]. The bronchodilator percentage change of 3.98%, 0.63%, and 20.72% was, respectively, documented for FEV1, FVC, and FEF_{25-75} [Figure 1]. The value of FEV/FVC (SD) when the mean value was calculated for all study participants was normal, 82.44% (7.34).

Categorized prebronchodilator response patterns of lung function abnormalities among children with human immunodeficiency virus

When the lung function outcome was categorized using the 1.64 Z-score cutoff that corresponds to the LLN, 76 participants (73%) had abnormal FEV1. There were 44 participants (42%) with abnormal FVC, while 54 (52%) had abnormal FEF_{25-75}. However, the FEV_1/FVC was normal in 77 (74.0%) of the study population, as shown in Table 4.

Categorized postbronchodilator response assessment of various lung functions and the abnormal forced expiratory volume in 1 s association with other lung function parameters

Postbronchodilator lung function parameters after salbutamol administration were also assessed. The FEV_1 is the most affected component in the majority of the children, which further served as the baseline to detect other underlying pathologies.

Forced expiratory volume in 1 s

Among all study participants, there were 55/104 (52.4%) of the children whose FEV1 showed positive BDR; and of these, more than half, 39/55 (70.9%) had low $zFEV_1$.

Table 2: Pattern of lung function and effect of bronchodilation

Lung function variable	FEV_1	FVC	FEF_{25-75}
Pre-BDR (Z-score value±SD)	−2.19±1.07	−1.86±1.17	−1.60±1.24
LLN±SD	2.12±0.61	2.42±0.70	2.09±0.53
Predicted±SD	2.62±0.74	2.96±0.86	3.17±0.79
Percentage predicted±SD	73.72±12.82	79.72±12.56	68.35±23.55
Post-BDR (Z-score value±SD)	−1.10±9.16	−1.82±1.26	−1.11±1.35
Percentage predicted±SD	75.44±15.43	80.1±13.66	78.14±26.02
BDR percentage change±SD	3.98±11.86	0.63±10.62	20.72±55.17

FEV_1=Forced expiratory volume in 1 s, FVC=Forced vital capacity, FEF_{25-75}=Forced expiratory flow between 25% and 75% of vital capacity, BDR=Bronchodilator response, SD=Standard deviation, LLN=Lower limit of normal

Table 3: Pre- and postbronchodilator lung function outcome in children with abnormal forced expiratory volume in 1 s

Lung function *Z*-scores	Mean±SD	*P*
FEV_1		
Pre-BDR	−2.19±1.07	0.001
Post-BDR	−1.97±1.17	
FVC		
Pre-BDR	−1.86±1.17	0.632
Post-BDR	−1.82±1.26	
FEF_{25-75}		
Pre-BDR	−1.60±1.24	<0.001
Post-BDR	−1.11±1.35	

FEV_1=Forced expiratory volume in 1 s, FVC=Forced vital capacity, FEF_{25-75}=Forced expiratory flow between 25% and 75% of vital capacity, BDR=Bronchodilator response, SD=Standard deviation

When the cutoff was at 15% change, 35 (63.6%) were BDR positive, and even when the cutoff bar was further raised to positive BDR of ≥20%, more than half of that population (29, 52.7%) with abnormally low FEV_1 were still BDR positive. The remaining 30% of the cohort with low $zFEV_1$ showed irreversible airway obstruction, i.e., abnormally low $zFEV_1$ with no substantial response to salbutamol. In all the children with abnormal FEV1, their mean lung function (pre- and post-BDR) showed that the $zFEV_1$ and $zFEF_{25-75}$ were the most affected [Table 5].

Forced expiratory volume/forced vital capacity

When assessed specifically, the values of FEV/FVC that measured 80% and above (mean of 82.44%) were found in 74% of the proportion of all study participants. Of these assessed children, 66.2% had abnormally low $zFEV_1$. Furthermore, 90.9% showed no significant change in FEV_1 with BDR using the 12% cutoff.

Forced vital capacity

Among all our participants, 57.7% had low zFVC. Among these, those who had both low $zFEV_1$ and nonsignificant BDR response were 59/60 (98.3%) and 52/60 (86.7%), respectively, suggesting a restrictive lung pathology.

Forced expiratory flow between 25% and 75%

Assessing the small airways using the value of $zFEF_{25-75}$ showed that about half of the study population had low $zFEF_{25-75}$, and all of them in this category had low FEV_1. The reversibility in that subset was also minimal as 42/50 (82%) had reversibility of less than 12%.

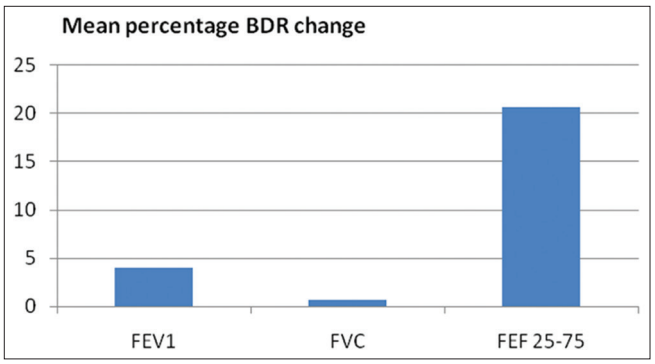

Figure 1: Mean bronchodilator response percentage change of various lung function parameters for all study participants

Risk factors for low forced expiratory volume in 1 s in children with human immunodeficiency virus

Except for nutritional status (Z-score for BMI [zBMI]), no other characteristics (age, gender, and social status) were significantly associated with low FEV_1 [Table 6].

Discussion

Despite abnormal lung function parameters suggestive of SAD in HIV-infected children, conventional parameters for assessing the pathology are inaccurate, costly, and rarely accessible. An accessible method of measuring these abnormal parameters, such as spirometry, will facilitate the early identification of SAD in these children.

In this study, we measured surrogate parameters of SAD such as FEV_1 and FEF_{25-75} which could identify the disease early in HIV-infected children. The reversibility of SAD was assessed by positive BDR in these lung function parameters. We demonstrated that different lung function abnormalities occur in these children, ranging from obstructive pathologies to restrictive, mixed, or fixed airway disease. When compared with the findings from a South African study,[14] our outcome lung function mean values were different. The authors reported much

Table 4: Pattern of prebronchodilator abnormalities in lung function

Categorized lung function variables (normal *Z*=>−1.64	FEV (%)	Pre-BDR FVC (%)	Pre-BDR FEF_{25-75} (%)	FEV/FVC (%)
Proportion with normal lung function	28 (26.9)	44 (42.3)	50 (48.1)	77 (74.0)
Proportion with abnormal lung function	76 (73.1)	60 (56.7)	54 (51.9)	27 (26.0)

FEV_1= Forced expiratory volume in 1 s, FVC=Forced vital capacity, FEV_1/FVC=Ratio of FEV_1 and FVC, FEF_{25-75}=Forced expiratory flow between 25% and 75% of vital capacity, SAD=Small-airway disease, BDR=Bronchodilator response normalize =>−1.64

Table 5: Mean lung function values analyzed for only children with abnormally low *Z*-score for forced expiratory volume in 1 s

Lung function *Z*-scores pre- and postbronchodilator testing	Mean±SD	*P*
FEV_1		
Pre-BDR	−2.63±0.79	0.003
Post-BDR	−2.37±0.99	
FVC		
Pre-BDR	−2.24±1.03	0.604
Post-BDR	−2.19±1.25	
FEF_{25-75}		
Pre-BDR	−1.99±1.14	<0.001
Post-BDR	−1.52±1.27	

FEV_1=Forced expiratory volume in 1 s, FVC=Forced vital capacity, FEF_{25-75}=Forced expiratory flow between 25% and 75% of vital capacity, BDR=Bronchodilator response, SD=Standard deviation

lower baseline mean Z-scores in HIV-infected children.[14] This finding may be explained by age-related study bias, the possibility of mixed-race population in their study location, and the utilization of the GLI reference equation for African Americans. Our study population was more homogenously black, which made us resort to the alternative GLI non-Caucasian "other" option.[16] In addition, the most affected lung function parameter was FEV_1, implying that many HIV-infected children are at risk of developing clinical manifestations of obstructive lung disease such as asthma. The FEF_{25-75} was also substantially abnormal, especially with deranged FEV_1. This observation suggests the possibility of SAD in many of these children. The FVC was notably the least affected. Thus, although some patients had restrictive or fixed airway lung abnormalities, they were not the predominant types within our cohort. Similar studies with larger sample sizes equally showed that obstructive lung disease was a prominent finding.[12,15,22]

The majority of our study participants had a normal FEV/FVC ratio which agrees with the pre-BDR findings in another related study,[14] where the cohort was predominantly children with asthma. However, a normal FEV/FVC ratio may not always signify a normal lung function but may suggest an obstruction in the presence of normal FVC. We noted that the majority had abnormal FEV_1 with normal FVC, indicating a possible early obstruction. The effect of low and declining FEV_1, if ignored in children with HIV, is further buttressed in the study by Ginthinji *et al*.[14] in which obstructive spirometry pattern increased from a prevalence of 4.8% at baseline to 8.1% at 24 months. In lung function assessment, FEV_1 as a drawback primarily reflects obstruction in the larger airways, and a significant degree of SAD precedes abnormalities in FEV_1.[6] We also found that among those with abnormalities in FEV_1 (even when positive BDR cutoff was made as high as 20%), more than half of those with abnormal FEV_1 remained positive, further showing that abnormal FEV_1 is to be expected in HIV-infected children. Interestingly, we also noted that when FEV_1 and FEF_{25-75} were both affected, there was higher certainty for the existence of SAD, coupled with the finding of higher proportion of BDR response for FEF_{25-75}. This finding occurred even in patients who initially failed to show abnormal FEF_{25-75}, thus unveiling possibilities of SAD.[23] This may imply that patients who have normal FEF_{25-75} but show a significant positive BDR in that regard should be potentially considered as having SAD and their other parameters such as FEV_1 immediately observed or further followed up on a long term. A similar study by Gingo *et al*.[13] revealed that only 21% of the participants had irreversible airway obstruction based on a postbronchodilator FEV_1/FVC ratio <0.70. Thus, restrictive abnormalities or fixed airway obstructions occur but may not be the significant abnormalities in this group of patients. We also observed that the participants concurrently showed irreversible airway obstruction and an abnormal $zFEV_1$ once they had low zFVC. Although abnormal $zFEV_1$ is prevalent in HIV-infected children, the patients' other parameters suggested restrictive pattern or fixed airway abnormality.

Where the usefulness of FEF_{25-75} as a marker of SAD remains doubtful, some authors still recognize that with a borderline value of FEV1/FVC, any abnormal FEF_{25-75} indicates the presence of airway obstruction.[24] Moreover, such FEF_{25-75} results have helped in the quality control of lung function assessments.[25] Pediatricians should, therefore, pay attention to FEF_{25-75} values in order to avoid missing SAD. Furthermore, assessment for associated risk factors showed a positive association with zBMI, suggesting that better nourishment (which may increase immunity) may serve as an additional protection from lung infections. The better weight and height, as well as higher zBMI scores, also mean better lung function values. Majority of our patients were reasonably well nourished with good mean zBMI score. Abnormal lung function parameters are thus basically due to the HIV-related effect on the lungs. In tandem with our observation, Arigiliani

Table 6: Effect of sociodemographic and nutritional factors on the lung function among outcome Forced expiratory volume in 1 s among children with human immunodeficiency virus

Variables	Lung function measured using FEV_1		Test statistic	*P*
	Normal (*n*=28), *n* (%)	Abnormal (*n*=76), *n* (%)		
Mean age in years (SD)	13.63 (3.07)	13.23 (3.29)	*t*=0.55	0.59
Gender				
Male	11 (37.0)	45 (56.2)	χ^2=2.89	0.09
Female	17 (63.0)	31 (43.8)		
Social class				
Class 1	4 (14.8)	6 (7.9)	χ^2=1.66	0.80
Class 2	5 (14.8)	10 (13.2)		
Class 3	4 (18.5)	21 (27.6)		
Class 4	11 (40.7)	27 (35.5)		
Class 5	3 (11.1)	12 (15.8)		
zBMI				
Normal	24 (85.2)	61 (80.3)	χ^2=5.59	0.05
Thinness	0 (0.0)	12 (15.7)		
Overweight	4 (14.8)	3 (4.0)		
HAZ				
Normal	27 (96.3)	63 (83.6)	FT	0.18
Stunted	1 (3.7)	13 (16.4)		

HAZ=Height for age *Z*-score, SD=Standard deviation, FEV_1=Forced expiratory volume in 1 s, zBMI=*Z*-score for body mass index, FT=F TEST i.e F Statistic = variance of the group means / mean of the within group variances

et al.,[26] using GLI methods, found that malnourished African children with normal FEV_1/FVC ratio concurrently had significant reductions in FEV_1 and FVC, supporting the positive correlation of nutrition and higher zBMI with lung function outcome.

Study limitations

Our sample size was small but was based on the calculated sample size using a previous study conducted in HIV-infected children, making it, nevertheless, appropriate for the study. We gathered information on the $CD4^+$ T-cell count and HAART for each child which may affect lung function outcome interpretation. These were not analyzed further as the enrolled patients were all stable and strictly adhered to HAART. Those who did not meet the inclusion criteria of clinical stability were excluded from participating, to minimize confounders that may affect the interpretation of results. The generalizability of the study findings to HIV-infected children who are not of the same ethnic group may appear as a limitation, but the use of GLI methods puts the ethnic correction into consideration and thus makes the data useful for African children with HIV.

Conclusion

Spirometric measurements in HIV-infected African children show that they have SAD. When there is an abnormal lung function parameter (particularly FEV_1), it is essential to look out for abnormalities in other parameters to help correctly interpret the modality of management. Every child with abnormal FEF_{25-75} (a marker of SAD) concurrently has abnormal FEV_1. The reversibility of FEF_{25-75} (shown by the positive BDR) was a prominent finding which should be a diagnostic priority. The intervention will help to triage patients that qualify for long-term follow-up of their lung function, especially where resources are scarce to perform routine spirometry on every HIV-infected child.

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Conflicts of interest

There are no conflicts of interest.

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