

Determinants of Severe Acute Malnutrition Among HIV-positive Children Receiving HAART in Public Health Institutions of North Wollo Zone, Northeastern Ethiopia: Unmatched Case–Control Study

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Background: Over half of the children living with HIV/AIDS suffer from severe acute malnutrition especially in countries having food insecurity like Ethiopia. However, determinants of severe acute malnutrition among HIV-positive children receiving care and treatment in antiretroviral therapy clinics in Ethiopia are not abundantly investigated. The aim of this study was to assess the determinants of severe acute malnutrition among HIV-positive children receiving highly active antiretroviral therapy in public health institutions of the North Wollo Zone, Northeastern Ethiopia.

Methods: An institutional-based unmatched case–control study was conducted on 204 under-fifteen, HIV-positive children (68 cases and 136 controls). The data were collected by reviewing medical records and by interviewing attendants. Binary and multiple logistic regressions were employed, and odds ratio with 95%CI was used to interpret results. A *p*-value of <0.05 was considered as a significant difference between cases and controls for the exposure variable of interest.

Results: A total of 204 under-fifteen, HIV-positive children were included in this study. Of them, 49.5% were males. About 79.4% of those children had acquired HIV infection through vertical transmission. Poor adherence to ART Adj-OR: 5.72 (1.08–30.27), duration on ART Adj-OR: 5.54 (1.44–21.24), severe immunodeficiency Adj-OR: 6.41 (1.09–37.86), advanced WHO clinical stage Adj-OR: 3.58 (1.03–12.43), oropharyngeal disease Adj-OR: 4.72 (1.13–19.73) and chronic diarrhea Adj-OR: 3.98 (1.05–15.04) were identified to be determinants of SAM in those children.

Conclusion: Determinant factors for SAM among HIV-positive children were chronic diarrhea, severe immunodeficiency, duration and adherence to ART, oropharyngeal disease and advanced WHO clinical stage. Therefore, it is better if interventions are developed and implemented to address these identified factors.

Keywords: HIV-positive children, severe acute malnutrition, determinants

Background

Malnutrition occurs when an individual fails to take or absorb enough essential nutrients due to different underlying factors, including infection as in HIV/AIDS. It manifests in three forms—as acute (wasting), chronic (stunting), or micronutrient

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Table 1 Sociodemographic and HIV-related Characteristics of HIV-positive Children Receiving HAART in Public ART Clinics of the North Wollo Zone, Northeastern Ethiopia, 2019

Variables		Frequency	Percentage
Sex (n=204)	Male	101	49.5
	Female	103	50.5
Age (n=204)	<5 years	39	19.1
	5–10 years	105	51.5
	>10 years	60	29.4
Vertical transmission (n=204)	Yes	162	79.4
	No	42	20.6
Exposure diagnosed (n=162)	Yes	126	77.8
	No	36	22.2
Prophylaxis for exposure (n=126)	Yes	126	100
	No	–	–
HAART regimen (within six months prior to SAM diagnosis) (n=204)	First Line	194	95.1
	Second Line	10	4.9
Duration on ART (n=204)	<49 months	105	51.5
	≥49 months	99	48.5
History of missing follow-ups (within six months prior to SAM diagnosis) (n=204)	Yes	53	26
	No	151	74
History of oropharyngeal disease (n=204)	Yes	29	14.2
	No	175	85.8
History of opportunistic infections (n=204)	Yes	117	57.4
	No	87	42.6
History of Chronic diarrhea (n=204)	Yes	32	15.7
	No	172	84.3
Adherence to ART (n=204)	Good	125	61.3
	Fair	55	26.9
	Poor	24	11.8
Orphan status (n=204)	Orphan	25	12.3
	Non-orphan	179	87.7
Caregiver for the child (n=204)	Yes	200	98
	No	4	2
Immunodeficiency status (lowest values within six months prior to SAM diagnosis) (n=204)	Severe	55	27
	Moderate	55	27
	Not significant	94	46
WHO clinical stage (highest stage within six months prior to SAM diagnosis) (n=204)	Stage I	38	18.6
	Stage II	85	41.7
	Stage III	63	30.9
	Stage IV	18	8.8

Abbreviations: ART, antiretroviral therapy; HAART, highly active antiretroviral therapy; SAM, severe acute malnutrition; WHO, World Health Organization.

deficiency. The acute form of malnutrition is again classified as mild, moderate or severe forms. Severe acute malnutrition (SAM) is an extreme and visible form

of malnutrition. It is characterized by very low weight for height Z-scores, severe muscle wasting, and nutritional edema.^{1,2}

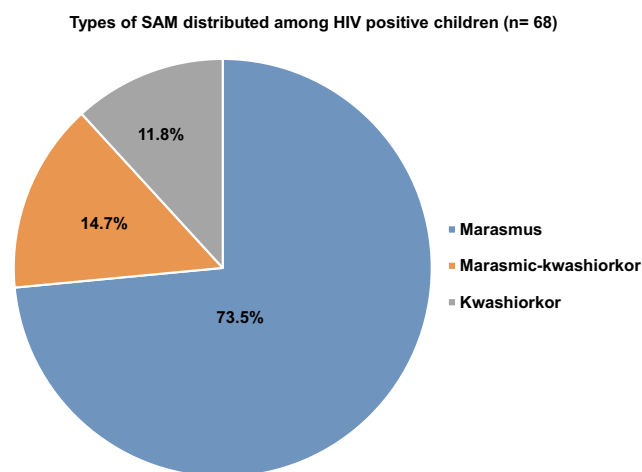


Figure 1 Types of severe acute malnutrition (SAM) distributed among under-fifteen, HIV-positive children with SAM, North Wollo Zone, Ethiopia, 2019.

Since, children are more vulnerable and at risk for different health-related conditions,³ HIV infection and malnutrition are major public health problems in children worldwide.^{2,4} In 2018, about 1.7 million under-fifteen children were infected with HIV worldwide,⁵ and more than 90% of them were found in Sub-Saharan Africa.⁶ Similarly, malnutrition is estimated to contribute to more than 20 million cases of childhood morbidity and mortality. Malnutrition is a major problem for HIV-infected children⁷ with a global prevalence of as high as 40%.⁸ Separately, malnutrition and HIV are prevalent in Ethiopia. In the country the prevalence of malnutrition in children reaches as high as 48%.⁹ Moreover, there were an estimated 710,000 people living with HIV among the general population and about 62,000 children in 2016.¹⁰ The prevalence of malnutrition among HIV-positive Ethiopian children is not abundantly investigated, but it is assumed to be high, especially in rural parts of the country.¹¹

Complex association exists between SAM and HIV infection. The two potentiate each other, because untreated HIV infection leads to repeated episodes of infection which contribute to loss of appetite and difficulty in eating. In turn, loss of appetite and difficulty in eating results in reduced food intake; predisposing the child to SAM. HIV/AIDS will also increase the severity of preexisting mild and moderate malnutrition cases.¹² Consequently, over half of the children living with HIV/AIDS will also suffer from SAM especially in countries having food insecurity like Ethiopia.^{13,14}

SAM causes oxidative stress and nutritional-acquired immune deficiency syndrome (NAIDS), which increases

the risk of progression of HIV infection to AIDS. Indeed, rapid progression to AIDS stage is more common even in well-nourished children, since they have physiologically immature immunity.^{15–17} In children with SAM, physiological and nutritional-acquired immune deficiency will act synergistically leading to acceleration of HIV progression and increased morbidity. Again, increased morbidity results in increased nutritional requirements. This complex association between the two factors will continue by creating a vicious cycle and the end result will be death of the sufferer.⁸

Due to this vicious cycle and complex interaction, SAM in HIV-positive children is an indicator of severe disease that is associated with a worse prognosis and impaired immune recovery even on antiretroviral therapy (ART).⁸ It will decrease adherence to ART, reduce effectiveness of ART, increase risk of opportunistic infections, facilitate HIV progression and shorten survival.^{18,19} Thus, among children with SAM, the risk of death is three to four times higher in HIV-infected children.^{20,21}

Improving nutritional status is a key strategy to reduce this increased risk of death and to prolong survival of HIV-infected children.²² Hence, different countries across the world including the Ethiopian Ministry of Health are implementing integrated nutritional and HIV care to improve nutritional status of infected individuals.^{6,23} But HIV/AIDS and SAM continue to be significant causes of death for children.⁷

Therefore, identifying determinants of SAM among HIV-positive children will aid proposing appropriate preventive and therapeutic strategies to improve nutritional status, increase the effectiveness of ART and to decrease morbidity and mortality in those children. Despite this few studies were conducted to address the issue, particularly in Ethiopia. Therefore, this study aimed to assess the determinants of SAM among HIV-positive children receiving highly active antiretroviral therapy (HAART) in public health institutions of the North Wollo Zone, Northeastern Ethiopia.

Methods

Study Design, Area and Period

An institution-based unmatched case-control study design was conducted from March to May 2019 in public ART clinics in the North Wollo Zone, Amhara Region, Northeastern Ethiopia. In this zone, there are 19 public health institutions that provide ART service for an estimated of 637 children under-fifteen.

Table 2 Multiple Logistic Regression Analysis for Determinants of Severe Acute Malnutrition Among HIV-positive Children, from a Study in the North Wollo Zone, Northeastern Ethiopia, 2019

Variables		Case	Control	Adj-OR (95%CI)
Sex of the child	Male	41	60	0.88 (0.3–2.8)
	Female	27	76	
Age of the child	<5 years	19	20	2.05 (0.6–7.6)
	≥5 years	49	116	
History of oropharyngeal disease	Yes	24	5	4.72 (1.1–19.7)*
	No	44	131	
History of opportunistic infections	Yes	51	66	2.83 (0.9–9.1)
	No	17	70	
History of chronic diarrhea	Yes	23	9	3.98 (1.05–15.0)*
	No	45	127	
HAART regimen	PI based	8	9	2.57 (0.4–17.1)
	Non-PI based	60	127	
Duration on ART	<49 months	48	57	5.54 (1.4–21.2)*
	≥49 months	20	79	
History of missing ART follow-ups	Yes	30	23	1.06 (0.3–4.1)
	No	38	113	
Level of adherence to ART	Good	25	100	2.29 (0.7–8.1) 5.72 (1.1–30.3)*
	Fair	24	31	
	Poor	19	5	
Immunodeficiency status	Not significant	10	84	2.07 (0.4–11.2) 6.41 (1.1–37.9)*
	Moderate	15	40	
	Severe	43	12	
Viral load	Undetectable	7	58	1.01 (0.2–6.5) 1.16 (0.2–8.3)
	<1000 copies	15	49	
	≥1000 copies	46	29	
WHO staging	Early (Stage I/II)	11	112	3.58 (1.03–12.4)*
	Advanced (stage III/IV)	57	24	
Orphan status of the child	Orphan (mother/father/both died)	15	10	3.02 (0.7–12.4)
	Nonorphan	53	126	
Family size	≤3	23	69	1.04 (0.3–3.2) 1.6 (0.2–14.0)
	4–6	38	60	
	≥7	7	7	
Household food security	Secured	60	128	1.37 (0.2–10.1)
	Not secured	8	8	

Note: *Significance at p -value <0.05 on multiple logistic regression model.

Abbreviations: Adj-OR, adjusted odds ratio; ART, antiretroviral therapy; COR, crude odds ratio; HAART, highly active antiretroviral therapy; PI, protease inhibitor; WHO, World Health Organization.

Study Population

All under-fifteen, HIV-positive children receiving HAART in ART clinics of the North Wollo Zone were the source

population. Cases were all under-fifteen, HIV-positive children with history of SAM and receiving HAART in selected Public Health Institutions of the North Wollo Zone and

controls were all under-fifteen HIV-positive children without SAM receiving HAART in selected public health institutions of the North Wollo Zone.

Eligibility Criteria

Under-fifteen HIV-positive children who had history of SAM (MUAC <11.5 cm, or weight for height/length Z-score <-3, or bilateral pitting edema of other causes excluded with or without severe wasting, or body mass index (BMI) Z-score <-3) were included as cases.

Under-fifteen, HIV-positive children who had no history of SAM were included as controls.

Children who had developed SAM before the diagnosis of HIV, medical records with deceased children and medical records with missed significant information were excluded from cases and controls. Children who were on ART for less than six months were also excluded; aimed to address HIV-treatment related factors.

Sample Size Determination and Sampling Techniques

The sample size was determined using a formula for two population proportion and calculated with Open Epi version 7.2.0.1 statistical software package by considering the following assumptions from a study conducted in South Africa:²⁴ proportion of controls exposed=51%, OR=2.72, power=80%, confidence level=95%, case to control ratio=1:2 and nonresponse rate=15%. This yields a total sample size of 204 (68 cases and 136 controls).

Samples were selected by simple random sampling technique (lottery method) by using their medical registration number as a sampling frame.

Study Variables

Severe acute malnutrition in HIV-positive children was the outcome variable and sociodemographic variables (age of the child, sex of the child, residence, availability of caregiver, orphan status, caregiver's age, caregiver's educational status, family size, household food security); child nutritional related variables (feeding frequency, food diversity, counseling on child nutrition); medical related variables (immunodeficiency status (CD4 count), viral load, WHO clinical stage, prophylaxis to exposure, HAART regimen, duration on HAART, missing follow-ups, adherence to HAART, opportunistic infections, chronic diarrhea (HIV enteropathy), oropharyngeal

disease, HIV status of the caregiver and being on ART) were the independent variables of the study.

Operational Definitions

HIV-Positive Children

Children aged <15 years with confirmed HIV infection.

History of SAM

Having at least one indexed case of physician diagnosed SAM or MUAC <11.5 cms, or weight for height/length Z-score <-3, or bilateral pitting edema of other causes excluded with or without severe wasting, or BMI Z-score <-3 with in the last one year prior to data collection.

History of Opportunistic Infections

A child with HIV-related infections other than chronic diarrhea and oropharyngeal disease; within the last six months prior to SAM diagnosis.

History of Chronic Diarrhea

A child with diarrheal disease of 30 days or more duration; within the last six months prior to SAM diagnosis.

History of Oropharyngeal Disease

A child with oral ulcer or candidiasis/oral thrush; within the last six months prior to SAM diagnosis.

Data Collection methods, Tools and Procedure

The data was collected by extracting available information from participant's medical record and by interviewing the participant's attendants/participants (mixed primary and secondary data was used). Data extraction checklists and semistructured questionnaires adapted from a previous study²⁵ were used and five data collectors working in ART clinics and five supervisors were recruited. Data collectors first took the informed consent. Then interviewing of volunteers and extraction of the required information from the participant's medical record was conducted.

Data Quality Control

The checklist and questionnaire were pretested on 10% of the sample size and necessary modifications were made to increase their quality for the actual data collection. The data collectors and supervisors were trained. During data collection, data collectors and supervisors had checked the checklist and questionnaire for completeness and had double-checked the checklist with the participant's medical record accordingly. The principal investigator had also checked the whole process

of data collection and lastly the data was checked during coding, data entry and was cross tabulated before analysis.

Data Entry and Analysis

After data collection and assuring of the data quality, the questionnaire was coded and data was entered in EpiData version 4.2.0. Then the entered data was exported to SPSS version 23 for analysis. Descriptive analysis was employed to describe sociodemographic characteristics of study participants and the type of SAM distributed among case groups. To identify determinants of SAM among HIV-positive children, first, binary logistic regression was used and variables that had a p -value of <0.25 were entered into multiple logistic regression for further analysis. Odds ratio with 95%CI was used to interpret results and a p -value of <0.05 was considered as significant difference between cases and controls for the exposure variable under study. Finally, results were presented in the form of narrative, tables, graphs and charts.

Results

Sociodemographic Characteristics and Medical Conditions of the Study Subjects

A total of 204 HIV-positive children were included in the study, of which 49.5% were males. Their ages ranged from 2–14 full years with a mean and standard deviation of 8.28 ± 3.55 years, and 19.1% of them were under-five years of age.

Among the 204 children 162 (79.4%) had acquired HIV infection from their mother (through vertical transmission). Among those vertically infected children 126 (77.8%) were diagnosed as HIV exposed during birth and had taken prophylaxis for exposure. All the study subjects were on HAART, and most of them (95.1%) were on a first-line HAART regimen. Their duration on ART ranged from 6–120 full months with a mean and standard deviation of 48.46 ± 30.68 months, and 26% and 11.8% of them had a recorded history of missing of their follow-ups and poor adherence to ART respectively. The majority of the children (60.3%) were at an early stage of HIV, while 8.8% had history of reaching WHO-Stage IV. Fifty-five children (27%) had a recorded history of severe immunodeficiency. Among the total 204 study subjects, 117 (57.4%), 32 (15.7%), and 29 (14.2%) had history of opportunistic infection, chronic diarrhea, and oropharyngeal disease/candidiasis respectively (Table 1).

Types of SAM Distributed Among HIV-positive Children

Marasmus was found to be the commonest type (50, 73.5%, where $n=68$) of SAM distributed among HIV-positive children (Figure 1).

Determinants of Severe Acute Malnutrition

On the binary logistic regression, 15 variables having a p -value of less than 0.25 were found and all of those variables were entered in to multiple logistic regression for further analysis. Among variables entered in to multiple logistic regression, there was significant difference in exposure for oropharyngeal disease, chronic diarrhea, duration on ART, adherence to ART, immunodeficiency and WHO clinical stage between cases and controls and those variables were found to be a determinant for SAM among HIV-positive children as they have a p -value of less than 0.05 (Table 2).

HIV-positive children with history of oropharyngeal disease were 4.7 times more likely to develop SAM than HIV-positive children without history of oropharyngeal disease Adj-OR: 4.72 (1.13–19.73). Similarly, HIV-positive children with history of chronic diarrhea were four times more likely to develop SAM than HIV-positive children without history of chronic diarrhea Adj-OR: 3.98 (1.05–15.04).

The odds of SAM among HIV-positive children with history of poor adherence to ART was 5.7 times more than HIV-positive children with history of good adherence Adj-OR: 5.72 (1.08–30.27). HIV-positive children who have duration on ART for less than 49 months were also 5.5 times more likely to develop SAM than HIV-positive children who have duration on ART for 49 months and above Adj-OR: 5.54 (1.44–21.24).

HIV-positive children with severe immunodeficiency were 6.4 times more likely to have SAM than HIV-positive children with nonsignificant immunodeficiency Adj-OR: 6.41 (1.09–37.86). HIV-positive children with advanced WHO clinical stage (stage III and IV) were also 3.6 times more likely to have SAM than HIV-positive children with early WHO clinical stage Adj-OR: 3.58 (1.03–12.43).

There was no significant difference (p -value ≥ 0.05) in exposure for age, sex, orphanhood, viral load, HAART regimen, missing follow-ups, opportunistic infection,

family size, and household food security among cases and controls.

Discussion

Various literature had revealed HIV/AIDS to be an independent and nonmodifiable risk factor for poor nutritional outcomes in those who are already infected and had identified different underlying factors.^{7,26,27} This study had also identified determinants of SAM among HIV-positive children by assessing exposure difference for sociodemographic, medical related and nutritional related factors among HIV-positive children with SAM (cases) and without SAM (controls) in the North Wollo Zone public ART clinics.

In this study, HIV-positive children with oropharyngeal disease/candidiasis were found more likely to develop SAM than HIV-positive children without oropharyngeal disease and it was in line with a study conducted in Gojjam, Ethiopia²⁵ and Douala, Cameroon.² Oropharyngeal diseases might take forms of oral ulcer or oral candidiasis or it could manifest with eating difficulties and would limit the child from taking enough food, which in turn predisposed the child to malnutrition. The literatures^{2,11,28} had shown that presence of eating problems as determining factors to develop malnutrition in HIV-positive children which were in agreement with the results of this study. HIV-positive children with chronic diarrhea were also more likely to develop SAM than HIV-positive children without chronic diarrhea. This result was consistent with studies conducted in Gojjam, Ethiopia²⁵ and Dar es Salaam, Tanzania.²⁹ This association might be justified by the reason that diarrhea would increase intestinal motility and affect nutrient absorption from the child's gut or it might affect the child's appetite. Subsequently, children with chronic diarrhea are prone to malnutrition.

HIV-positive children with advanced WHO clinical stage of HIV were also more likely to have SAM than HIV-positive children with early an stage. The result was similar with studies conducted in Tanzania²⁹ and Thailand²⁷ as they showed advanced WHO stage of HIV to be associated with malnutrition. This study had also revealed that immunodeficiency status to be a determinant factor for SAM in HIV-positive children; which was in line with a study conducted in seven countries of central and West Africa.³⁰ But it was different from studies conducted in Thailand²⁷ and India³¹ as they had stated the association between malnutrition and immunodeficiency status in HIV-positive children to be insignificant. This difference might be due to variation in study design as those were cross-sectional studies.

The odds of SAM were higher among HIV-positive children with poor adherence and in children with duration on ART shorter than the mean duration (<49 months) of children studied. This was in line with a study conducted in Pediatric ART clinics of Felege Hiwot and Gondar referral hospitals, Ethiopia.¹¹ But, a study conducted in Thailand²⁷ had revealed malnutrition among HIV-positive children had no significant association with adherence to ART. This contradiction might be due to difference in children's adherence level between Thailand and Ethiopia; as more than 82% of the children in Thailand had good adherence to ART, while only 61.3% children having good adherence were identified in this study. Antiretroviral therapies are intended to limit viral replication and progression of HIV infection to advanced stages.¹⁹ But this occurs when an individual with HIV takes those therapies appropriately with good adherence and for longer durations. So, HIV-positive children who had not adhered to ART or had not taken ART for longer durations might be prone to progression of HIV to advanced stages, which in turn predisposed them to complications including malnutrition.

In contradiction with cross-sectional studies conducted in East and West Gojjam zones²⁵ and Adama Hospital Medical College in Ethiopia,²⁸ sex of the child was not a determinant for SAM among HIV-positive children. This contradiction might be due to differences in study design. However, this finding was similar to studies conducted in Felege Hiwot and Gondar referral hospitals, Northwest Ethiopia,¹¹ Cameroon,² and India,³¹ as they had revealed the association between malnutrition and sex was insignificant in HIV-positive children. In this study, there was no significant difference on household food security, feeding frequency and food diversity between cases and controls. This might be due to recruitment of samples living almost in districts having comparable socio-economic and cultural practices.

In this study viral load was not associated with SAM among HIV-positive children and the result was in line with a study conducted in India.³¹ Similarly, the existence of opportunistic infection was not associated with SAM among HIV-positive children in this study and was comparable to a study conducted in Pediatric ART clinics of Felege Hiwot and Gondar referral hospitals, Ethiopia,¹¹ but it was in contradiction with studies conducted in Parirenyatwa Group of Hospitals, Zimbabwe⁷ and East and West Gojjam, Ethiopia.²⁵ This contradiction might be due to differences in definition for opportunistic infection between this study and those studies—meaning this study used the term opportunistic infection for HIV-related infections other than chronic diarrhea

and oropharyngeal disease, while those studies include chronic diarrhea and oropharyngeal disease as opportunistic infections.

Strength and Limitations of the Study

This study had revealed HIV-infection and HIV-treatment related determinants of SAM in under-fifteen, HIV-positive children. But, the observed values for some explanatory variables were small (less than 30) and this makes the observed confidence interval to be quite larger. Multicollinearity test, correlation matrix, and multiple logistic model were used to control confounding effects; but, the unmatched nature of this study might pose a bias, despite those efforts.

Conclusion and Recommendations

There was significant difference in duration on ART, adherence to ART, immunodeficiency, chronic diarrhea, WHO clinical stage of HIV and oropharyngeal disease between cases and controls. Therefore, strategies targeted to increase adherence to ART, prevention and early treatment of diarrhea and oropharyngeal disease, and attendants'/children's commitment on adherence to ART are crucial to decrease the magnitude of SAM in HIV-positive children. Future research addressing the limitations of this study should be encouraged.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval and Consent to Participate

The study was approved by the Institutional Review Board (IRB) of College of Medicine and Health Sciences, Addis Ababa University with a protocol number of 036/19/SNM. The data was collected after taking written informed consent from the mothers/caregivers. Assent/affirmative agreement was also obtained from children aged ≥ 12 years. Study participants/attendants were also informed for the attainment of confidentiality and the information they give did not contain their name or any identifiers. This study was conducted in accordance with the Declaration of Helsinki.

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Author Contributions

All authors made substantial contributions to conception and design, analysis and interpretation of data; took part in drafting the article, revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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