

Delay in the Provision of Antiretroviral Therapy to HIV-infected TB Patients in Nigeria

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Abstract Background: Nigeria has a high burden of HIV and tuberculosis (TB). To reduce TB-associated morbidity and mortality, the World Health Organization recommends that HIV-positive TB patients receive antiretroviral therapy (ART) within eight weeks of TB treatment initiation, or within two weeks if profoundly immunosuppressed ($CD4 < 50$ cell/ μ L). **Methods:** TB and HIV clinical records from facilities in two Nigerian states between October 1st, 2012 and September 30th, 2013 were retrospectively reviewed to assess uptake and timing of ART initiation among HIV-positive TB patients. Healthcare workers were qualitatively interviewed to assess TB/HIV knowledge and barriers to timely ART. **Results:** Data were abstracted from 4,810 TB patient records, of which 1,249 (26.0%) had HIV-positive or unknown HIV status documented, and the 574 (45.9%) HIV-positive TB patients were evaluated for timing of ART uptake relative to TB treatment. Among 484 (84.3%) HIV-positive TB patients not already on ART, 256 (52.9%, 95% CI: 45.0-60.8) were not initiated on ART during six months of TB treatment. 30.0% of 273 patients with a known $CD4 \geq 50$ cells/ μ L started ART within eight weeks, and 14.8% of 54 patients with a known $CD4 < 50$ cells/ μ L started within the recommended two weeks. Only 42% of health workers interviewed reported knowing to interpret guidelines on when to initiate ART in HIV-positive TB patients based on CD4 cell count results. CD4 cell count significantly predicted timely ART uptake. **Conclusion:** A large proportion of HIV-positive TB patients were not initiated on ART early or even at all during TB treatment. Retraining of staff, and interventions to strengthen referral systems should be implemented to ensure timely provision of ART among HIV-positive TB patients in Nigeria.

Keywords Tuberculosis, HIV, Tuberculosis and HIV co-infection, Anti-retroviral Therapy, DOTS

1. Introduction

Tuberculosis (TB) and HIV are the two leading causes of death from infectious diseases in resource-limited countries [1]. The HIV epidemic has led to a major upsurge in TB cases worldwide, especially in Africa, as people living with HIV (PLHIV) who are infected with TB are much more likely to develop TB disease than those who are HIV-negative. Nigeria, in particular, has about 3.5 million PLHIV, an HIV prevalence of 3.1% among adults aged 15-49 years, and the highest number of AIDS-related deaths in the world [2]. In addition, in 2015 the World Health Organization (WHO) ranked it among the six countries that contribute 60% of the world's TB burden [1]. The same year, the HIV positivity rate among TB patients with a documented HIV test result was 17% [1].

The updated 2012 WHO strategic framework for TB/HIV collaborative activities highlights specific activities to reduce HIV-associated TB, including intensified TB case finding, isoniazid preventive therapy and TB infection control for PLHIV, as well as provider initiated HIV counseling and testing for TB patients, with early antiretroviral therapy (ART) uptake for co-infected patients [3]. Several clinical trials have demonstrated survival benefit due to early initiation of ART among HIV-infected patients with TB, particularly among those with very low CD4 cell counts [4-8]. Based on this evidence, WHO guidelines recommend that all HIV-positive TB patients receive ART within eight weeks of TB treatment initiation, or within two weeks if profoundly immunosuppressed ($CD4 < 50$ cell/ μ L) [3].

In Nigeria, there has been remarkable progress in the implementation of collaborative TB/HIV activities over the past few years. Guidelines published by the national TB/HIV technical working group of the Federal Ministry of Health (FMOH) prescribed the initiation of all TB/HIV patients on ART, irrespective of CD4 cell count, with timing in line with WHO recommendations [9].

This study aimed to assess uptake of ART among HIV-positive TB patients in Nigeria, the timing of ART initiation in relation to TB treatment, and TB treatment outcomes of co-infected patients. Through in-depth interviews provider perceptions and current practices of patient referral systems were also ascertained. Findings will assist the FMOH and President's Emergency Plan for AIDS Relief (PEPFAR)-funded implementing partners to develop effective interventions to improve access to and quality of TB/HIV care and treatment services in Nigeria. They also establish a baseline for monitoring future progress of TB/HIV programme implementation.

2. Methods

Study Design and Sampling

This evaluation involved a retrospective review of TB and HIV clinical records for adult TB patients aged 15 years and above who enrolled in all TB Directly Observed Therapy (DOT) facilities in Federal Capital Territory (FCT) and Ogun State between October 1, 2012 and September 30, 2013. Health facility TB registers and additional supplemental TB data sources such as Presumptive TB registers, TB treatment cards, and Local Government Area TB registers were reviewed to determine the total number of TB patients seen in 2013 with an HIV status recorded as positive or unknown. These patients were traced to HIV facilities to ascertain their treatment status and timing of ART initiation relative to TB treatment, using HIV care cards and ART registers. In both states, all PEPFAR-supported ART treatment facilities that were providing ART services as of October 1, 2012 were included. In FCT there were 16 facilities and in Ogun State there were 28.

In-depth interviews were conducted with 333 key health care workers selected randomly across all the study facilities using a semi-structured questionnaire, in order to assess knowledge and practices related to TB/HIV management as well as provider perceptions about the barriers to provision and uptake of ART.

Data Collection and Analysis

Data were collected using a specifically designed data abstraction form that captured demographics, TB and HIV treatment, timing of ART, and TB treatment outcome information, following a retrospective review of the existing TB and HIV clinical and program recording and reporting systems. Descriptive statistics, including frequencies and percentages were used to summarize the data, and 95% confidence limits for all statistics were computed, taking into account the design effect resulting from within-clinic correlation. Unadjusted and adjusted odds ratios (ORs and AORs) and 95% confidence intervals (CI) were calculated to

describe associations between categorical variables and ART uptake. Multiple logistic regression was used to assess for predictors of timely ART uptake. We defined 'timely ART' per WHO guidelines as ART started within two weeks of TB treatment initiation for patients with a CD4 cell count $<50\text{cells}/\mu\text{L}$, and within eight weeks for all other cases. For the purposes of the multivariate analysis, we also considered ART initiation to have been timely for patients with a missing CD4 cell count only if it was started within two weeks, presuming that in the absence of a CD4 test the patient should be treated sooner rather than later. SAS 9.3[®] (SAS Institute, Cary, NC) was used with procedures designed to account for clustered data, such as PROC SURVEYFREQ and PROC SURVEYLOGISTIC. The in-depth interviews were transcribed, coded, and thematically analyzed.

Ethical Considerations

The protocol and all supporting data collection tools were reviewed by the United States Centers for Disease Control and Prevention (CDC) Associate Director for Science and the Nigeria Research and Ethics Committee, and was determined as a non-research program evaluation as the study involved the use of routine programmatic data with minimal risk to subjects.

3. Results

Baseline Characteristics of Study Participants

Data were abstracted from a total of 4,810 TB patients from 44 DOTS sites in FCT and 70 in Ogun State. These were made up of 1,249 TB patients with a positive or unknown HIV status (574 and 675, respectively). Of the HIV-positive TB patients, median age was 36 (interquartile range [IQR] 30-43), 308 (54.1%) were female, and median CD4 cell count was $178\text{cells}/\mu\text{L}$ (IQR: 80-298) (Table 1). Most of these patients were between ages 25-44 (69.5%), and seen within secondary health care facilities (55.7%). Three hundred and fifty-one (65.9%) accessed DOT at health facilities while 182 (34.2%) had TB treatment supporters for treatment at home. Two hundred and forty six (44.7%) had pulmonary smear-positive TB, 277 (50.4%) had pulmonary smear-negative TB, and 27 (4.9%) had extra-pulmonary TB. The majority of patients were new TB cases (92.9%) (Table 1).

Timing of ART Uptake among TB/HIV Co-infected Patients

Among 574 HIV-positive TB patients evaluated, 90 (15.7%, 95% CI: 7.1-24.2) had already started ART before TB treatment, while 256 (44.6%, 95% CI: 35.9-53.3) were not documented to have initiated on ART during the

six-month course of TB treatment at all. CD4 cell count was missing for 199 patients (34.7%). Of the 273 patients with a known CD4 cell count greater than or equal to 50cells/ μ L who were not already on ART when they started TB treatment, 82 (30.0%, 95% CI: 22.4-37.7) started ART within the recommended eight weeks of TB treatment initiation, while 60 (22.0%, 95% CI: 12.4-31.5) started ART during TB treatment but only after eight weeks. Among the 54 patients with a CD4 cell count <50cells/ μ L who were not

already on ART at the time of TB treatment initiation, only eight (14.8%, 95% CI: 6.6-23.0) commenced ART within the recommended two weeks of TB treatment initiation, and 21 others (38.9%) started ART, but after two weeks had passed. The remaining 25 (46.3%) were not documented to have started ART at all while on TB treatment (Table 2). Of these 25, 14 achieved TB cure or treatment completion, three defaulted, three died, four transferred out and one had no TB treatment outcome reported.

Table 1. Demographic and Clinical Characteristics of Study Participants

Variable	N	%
Age (N=574)		
15-24	49	8.5
25-34	183	31.9
35-44	216	37.6
45-54	96	16.7
\geq 55	30	5.2
Gender (N=569)		
Male	261	45.9
Female	308	54.1
Baseline CD4 (cells/μL) (N=574)		
0-49	61	10.6
50-199	147	25.6
200-499	141	24.6
\geq 500	26	4.5
Missing	199	34.7
TB Facility Type (N=571)		
Primary	112	19.6
Secondary	318	55.7
Tertiary	141	24.7
Type of DOT services (N=533)		
Health facility	351	65.9
Home (treatment supporter)	182	34.1
TB Disease Classification (N=550)		
Pulmonary smear positive	246	44.7
Pulmonary smear negative	277	50.4
Extra-pulmonary	27	4.9
TB Patient Category (N=562)		
New	522	92.9
Relapse	11	2.0
Return after default	3	0.5
Transfer in	15	2.7
Prior treatment failure	1	0.2
Other*	10	1.8
TB Treatment Outcome (N=558)		
Cured	115	20.6
Completed	274	49.1
Failure	6	1.1
Default	62	11.1
Died	60	10.8
Transfer out	41	7.3

* TB patient with unknown previous TB treatment history

Table 2. Timing of ART Uptake after the Start of TB Treatment Initiation, among Co-infected Patients

Timing of ART Initiation	CD4 <50		CD4 ≥50		CD4 Missing		All Patients	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Before TB treatment (Rx)	7	11.5 (0.6-22.3)	41	13.1 (3.3-22.8)	42	21.1 (12.3-29.9)	90	15.7 (7.1-24.2)
<2 weeks since TB Rx initiation	8	13.1 (5.2-21.0)	28	8.9 (5.4-12.4)	19	9.5 (5.6-13.5)	55	9.6 (6.9-12.3)
2-8 weeks since TB Rx initiation	13	21.3 (8.7-34.0)	54	17.2 (12.3-22.1)	21	10.6 (4.8-16.3)	88	15.3 (11.2-19.5)
>8 weeks since TB Rx initiation	8	13.1 (5.2-21.0)	560	19.1 (11.1-27.1)	17	8.5 (3.9-13.2)	85	14.8 (9.8-19.8)
No ART during 6 months TB Rx	25	41.0 (25.9-56.0)	131	41.7 (31.1-52.3)	100	50.3 (37.2-63.3)	256	44.6 (35.9-53.3)
TOTAL	61		314		199		574	

Table 3. Factors associated with *Timely ART provision to HIV-infected TB patients.

Variable	N (%)	OR(95% CI)	p-value	AOR(95% CI)	p-value
Sex			.2507		-
Male	53 (24.8)	1.29 (0.83-2.00)			
Female	54 (20.3)	<i>ref</i>			
Age			.0220		.0795
15-24	7 (17.1)	0.44 (0.15-1.27)		0.68 (0.26-1.78)	
25-34	31 (19.4)	0.51 (0.24-1.09)		0.59 (0.27-1.29)	
35-44	37 (21.0)	0.56 (0.28-1.14)		0.62 (0.31-1.28)	
45-54	25 (31.7)	0.98 (0.46-2.10)		1.10 (0.48-2.50)	
≥ 55	9 (32.1)	<i>ref</i>		<i>ref</i>	
TB Patient Category			.0853		.2011
New	104 (23.2)	1.81 (0.92-3.57)		1.69 (0.76-3.76)	
Other	4 (14.3)	<i>ref</i>			
TB Classification			.8448		-
Pulmonary smear +	48 (22.6)	1.32 (0.36-4.83)			
Pulmonary smear -	55 (23.7)	1.40 (0.44-4.45)			
Extra-pulmonary	4 (18.2)	<i>ref</i>			
Baseline CD4			.0010		.0012
<50/μL	8 (14.8)	<i>ref</i>		<i>ref</i>	
50-199/μL	41 (32.3)	2.74 (1.41-5.31)		2.67 (1.36-5.22)	
200-499/μL	40 (32.8)	2.81 (1.31-6.02)		2.74 (1.22-6.15)	
≥500/μL	1 (4.2)	0.25 (0.03-1.91)		0.25 (0.03-1.87)	
Missing	19 (12.1)	0.79 (0.40-1.57)		0.79 (0.39-1.61)	
Type of DOT services			.9512		-
Health Facility	66 (23.0)	0.98 (0.56-1.74)			
Home	38 (23.3)	<i>ref</i>			
TB Outcome			.2588		-
Cured or Completed	82 (24.8)	1.57 (0.67-3.69)			
Failure or Default	8 (15.1)	0.85 (0.29-2.46)			
Transfer out	7 (20.0)	1.19 (0.35-3.69)			
Died	9 (17.3)	<i>ref</i>			

*Timely ART provision was defined as within two weeks for patients with a CD4 <50cell/μL or missing, and as within eight weeks for all others.

Factors Associated with Timely ART Uptake among Co-infected Patients

In our multivariate analysis, CD4 cell count was found to be the only factor associated with Timely ART provision (using the previously stated definition of “timely ART provision”), with AORs of 2.7 (95% CI: 1.4-5.3) and 2.7 (95% CI: 1.2-6.2) for CD4 cell count categories 50-199cells/ μ L and 200-499/ μ L, respectively, when compared with having a CD4 cell count less than 50cells/ μ L (Table 3).

TB Treatment Outcomes for HIV-Positive Patients

TB treatment outcome was documented for 558 (97.4%) of patients with a positive HIV status (Table 1). Seventy eight percent of patients with a CD4 cell count \geq 50cells/ μ L had documented cure or treatment completion (a positive outcome), compared with 63.2% of those with CD4 cell count $<$ 50cells/ μ L and 57.2% of those with a missing CD4 cell count. Removing the 41 patients who transferred out, the odds of a positive outcome for patients with a CD4 cell count \geq 50cells/ μ L was 2.6 (95% CI: 1.6-4.3) times that for patients with a missing CD4 cell count, but not significantly higher than for patients with a CD4 $<$ 50cells/ μ L. For patients with documented treatment failure or default, median time to this outcome was 67.0 days (IQR: 43.0-141.1) for the eight patients (11.8%) with CD4 $<$ 50/ μ L, 93.0 days (IQR: 63.0-154.0) for the 30 patients (44.1%) with CD4 \geq 50cells/ μ L, and 72.0 days (IQR: 27.5-119.0) for the 30 patients (44.1%) with a missing CD4 cell count. Median time to death of those who died during follow up was 41 days (IQR: 34.0-53.0) for the six patients (10.0%) with

CD4 $<$ 50cells/ μ L, 55.0 days (IQR: 41.0-99.0) for the 22 (36.7%) with CD4 \geq 50cells/ μ L, and 30.0 days (IQR: 4.0-53.0) for the 32 (53.3%) with a missing CD4 cell count.

Healthcare Worker Perceptions of Barriers to Timely ART Uptake for HIV-Infected TB Patients

Semi-structured interviews were conducted with 333 health care workers to assess their perceptions and current practices of patient referral between TB and HIV programs and facilities (Table 4). Of 312 interviewees that responded to the question on which TB/HIV service delivery model was used in their facility, 125 (40.1%) worked in a facility with an integrated TB/HIV service delivery model. Of 240 respondents, 137 (57.1%) reported having CD4 services available. The preferred mode of referral of patients between HIV and TB services was by escort (40.1%) followed by use of referral slips (38.4%). Most of the staff interviewed (84.4%) reported having TB/HIV guidelines available, however only 59.6% of 285 respondents reported prior training on TB/HIV. Additionally, only 38.8% of 242 respondents reported adhering to recommendations for ART initiation in TB/HIV co-infected patients irrespective of CD4 count, and only 41.9% knew that patients with a CD4 less than 50cells/ μ L should start ART within two weeks of TB treatment initiation.

Key recommendations from healthcare worker respondents for improving TB/HIV services for patients ranged from capacity building for health care workers (12.4%), proper patient follow up (19.0%), to patient counseling and health education (38.5%).

Table 4. Healthcare Worker Interview Responses (N=333)

	N	%
Cadre of Healthcare Staff Interviewed (N=333)		
Doctors	50	15.0
Nurse	108	32.4
Pharmacists	10	3.0
Lab Scientists	13	3.9
Community Health Workers	100	30.0
Medical Records staff	15	4.5
Counsellors	16	4.8
Others	21	6.3
Reported Facility Characteristics		
Has TB diagnostic services (AFB) available (N=178)	175	98.3
TB/HIV service delivery model (N=312)		
Stand-alone TB facility	133	42.6
Stand-alone ART facility	54	17.3
Integrated TB/HIV facility	125	40.1
CD4 available at site (N=240)	137	57.1
Distance to referral site for TB diagnosis (n=136)		
Less than 5Km	56	41.2
6-10Km	39	28.7
10-20Km	29	21.3
Over 20Km	12	8.8
Method of TB patient referral for HIV services (N= 232)		
Physical escort	93	40.1
Referral slip/directed to ART site	89	38.4
Given an appointment	19	8.2

Don't know/other	31	13.4
Healthcare Worker TB/HIV Knowledge and Management		
Reports past training on TB/HIV (N=285)	170	59.6
Reports past training on HIV testing for TB patients (N=207)	191	92.2
Reports available TB/HIV guidelines (N= 282)	238	84.4
Reports available guidelines on HIV testing for TB patients (N=282)	238	84.4
Identification of PLHIV for TB evaluation (N=265)		
Every patient	83	31.2
Presumptive TB patients only	139	52.5
Don't know/other	43	16.2
Asks adult TB patients about child contacts (N=264)	249	94.3
Interpretation of guidelines for ART in TB/HIV patients (N=242)		
ART initiation based on CD4	101	41.7
ART initiation irrespective of CD4	94	38.8
Don't know/other	47	19.4
Interpretation of guidelines for patients with CD4<50 (N= 236)		
Immediate within 2 weeks	99	41.9
Deferment till after 2 months of TB Rx	39	16.5
Initiation based on clinical judgement	39	16.5
Don't know/Other	59	25.0
Opinion on how to improve TB case detection (N=339)		
Implement active TB case finding	155	45.7
Improve on TB contact tracing	9	2.7
Opinion on how to ensure TB/HIV patients enroll in care (N= 221)		
Practice same day enrollment	133	60.2
Don't know/Other	88	39.8
Opinion on how to ensure ART started within 8 weeks (N= 215)		
Given appointment at start of TB	86	40.0
Use of reminders	30	14.0
Tracked home on missed appointment	37	17.2
Don't know/Other	62	28.8
Opinion on how to ensure TB/HIV patients remain on ART (N=216)		
Provide adherence support	141	65.3
Use of treatment supporter	23	10.6
Don't know	39	18.1
Other methods	24	11.1
Recommendations for service improvement (N= 226)		
Referral/proper patient follow up	43	19.0
Counseling and health education	87	38.5
Campaign and awareness	3	1.3
Capacity building for HCWs	28	12.4
Establishment of same site services	5	2.2
Mixed responses of the above and others	64	28.3

4. Discussion

Our study shows that almost 45% of HIV-positive TB patients (55% ART uptake) were not documented to be started on ART before or during their six-month course of TB treatment, despite WHO and Nigerian guideline recommendations. The study participants were selected from DOTS sites across primary, secondary and tertiary health facilities in Ogun State and FCT, Nigeria. This proportion is much higher than the 67% ART uptake reported by WHO for Nigeria within same study period, and also higher than reported elsewhere in sub-Saharan Africa in settings where TB and HIV services were not integrated, WHO TB Report [10-14]. Possibly, this could indicate poor documentation of ART initiation in charts in our sampled health facilities, or ART initiated after TB treatment completion. Interviewed

healthcare workers in this study also identified poor linkage between TB and HIV services as barrier to timely ART initiation for HIV-positive TB patients. To address this problem, the Nigerian FMOH has since introduced TB/HIV referral coordinators within high volume ART sites to support referral linkages between DOTS and ART sites so as to improve service uptake among TB and HIV co-infected patients.

The approximately 85% of our HIV-positive TB patients who were not already on ART at the time of TB treatment initiation – if they started ART at all during the course of TB treatment – were not likely to do so within the recommended timeframe. Less than a third of patients with a CD4 \geq 50cell/ μ L started ART within the recommended eight weeks, and only 15% of those with a CD4<50cell/ μ L started within the recommended two weeks. Almost half of this

latter, highly immunocompromised group was not reported to start ART at all during TB treatment, even though the majority of them lived and were followed until successful TB treatment or cure, indicating a window of opportunity to start timely ART that was not prematurely cut short due to loss-to-follow-up or death. This is far behind what has been reported in similar settings in Africa [15-17].

A documented CD4 cell count was missing for 35% of patients. For the more than 40% of health workers interviewed who reported basing their decision to initiate ART on CD4 cell count results, this is problematic. However, this practice is counter to recommended guidelines to begin ART in HIV-positive TB patients irrespective of CD4 cell count, and is likely a major barrier to timely ART uptake. For those that did have a CD4 cell count reported, a CD4 cell count greater or equal to 50cells/ μ L significantly predicted timely ART, as well as TB treatment completion or cure. The former finding is similar to those from a collaborative analysis of data from South African cohorts, which found that the overall time to starting ART was strongly associated with patient CD4 cell counts [12]. It is important to note that we expected a shorter time to ART initiation for people with lower CD4 counts, and defined "timely ART" differently based on a CD4 cutoff of 50cell/ μ L; this, while perhaps influencing the likelihood of meeting the expected timeframe, is appropriate based on WHO and Nigerian guidelines. Unfortunately, only 40% of healthcare workers interviewed knew that patients with lower CD4 cell counts should start ART earlier. Clearly, additional training and supportive supervision of health care workers in ART clinics is required.

Overall, almost 70% of co-infected patients had documented TB treatment completion or cure, which reflects the global average [1]. Timely ART initiation relative to TB treatment was not significantly associated with TB treatment outcomes at six months. This has been shown elsewhere, although several randomized controlled trials have demonstrated that early ART improves survival for those with very low CD4 cell counts [5, 6, 18-21]. The odds of a positive TB treatment outcome were, however, more than twice as high for those with CD4 cell counts greater than 50cells/ μ L than for those with a missing CD4 cell count. Median time to death, treatment failure or default was not significantly different between these groups, indicating that this finding is not simply due to higher rates of death or loss to follow up for those with a missing CD4 cell count.

The key strength of this study was that it assessed routine programmatic data from all types of TB treatment sites, supplemented with in-depth interview with health care workers that provided insights into program challenges and recommendations for improvement. However, some limitations exist. Sites were not nationally representative, patients were not tracked to non-PEPFAR ART facilities and poor documentation in some facilities led to missing data. We were not able to disaggregate findings based on

co-located versus stand-alone TB and HIV facilities, and were only able to follow patients for the six-month duration of their TB treatment course to determine ART uptake.

Overall, this assessment demonstrates unacceptably low levels of timely ART uptake among HIV-positive TB patients in Nigeria, and provides important programmatic feedback to the Nigerian FMOH. Fully integrated TB and HIV service delivery, retraining of staff, ensuring adherence to guidelines recommendations, and interventions to strengthen referral systems should be implemented to ensure timely provision of ART to all HIV-positive TB patients in Nigeria, thus reducing morbidity and mortality and advancing efforts to achieve the ambitious 90-90-90 targets.

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Author Contributions

A.D., K.D. and B.O. conceived and designed the study; B.O., K.D., A.D., O.O., D.O., N.C. and S.D. developed the study tools and protocol; B.O., I.P., O.O., S.D., E.O and, E.E. trained research assistants and supervised data collection; S.P., J.O. and E.O. analyzed the data; B.O., I.P and S.P. drafted and edited the paper and K.D., S.P., A.D., D.O., O.O., J.O., E.O., D.S., E.E., N.C., P.D. and H.T. reviewed the paper.

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Conflicts of Interest

We report no conflicts of interest to disclose.

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