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ORIGINAL RESEARCH

Real-world prevalence of integrase inhibitor resistance and virological failure since adoption as guideline-preferred therapy

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Abstract

Background: Limited data reporting real-world prevalence of integrase strand transfer inhibitor resistance (INSTI-R) in the USA are available because their recommendation as first-line treatment in 2017. Reported national surveillance data in the USA estimated INSTI-R to be 6.3% as of 2018. This article aims to describe estimated prevalence of INSTI-R within a single clinic network in Chicago, IL, USA, and identify risk factors for resistance and virological failure (VF).

Methods: This was a retrospective, single-centre study of adults with HIV starting an INSTI-containing regimen between September 2017 and 2020. The primary endpoint was the difference in INSTI-R of the sample population compared with the national prevalence. Other outcomes included VF and documented INSTI-R mutations.

Results: Of 948 participants screened, 321 were included. Eight people had baseline INSTI-R testing results available, of which five had INSTI-R at baseline for an estimated prevalence of 1.6%. This estimation was significantly less than the national estimated prevalence of 6.3% ($p<0.001$). VF occurred in 26 (7.8%) individuals. Because no participants acquired INSTI-R during the study period, investigators were unable to identify risk factors associated with the development of INSTI-R. People with high pre-treatment viral loads had 1.21 (95% CI 1.05–1.39) higher odds of VF.

Conclusions: Amongst participants on INSTI-containing regimens, INSTI-R rates were estimated to be lower than the estimated national prevalence. Detectable pre-switch viral loads were more associated with VF than undetectable viral loads.

Keywords: antiretroviral therapy, HIV/AIDS, integrase inhibitors, resistance mutations.

Citation

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Introduction

The Department of Health and Human Services (DHHS) guidelines for the treatment of HIV in adult and adolescent persons recommend the use of a second-generation integrase strand transfer inhibitor (INSTI), namely bictegravir (BIC) or dolutegravir (DTG), as the anchor drug for first-line initial regimens in most people.[1] The initial recommendation of only second-generation INSTIs as first-line therapy occurred in late 2017. INSTIs are well tolerated and associated with achieving virological suppression more rapidly than other antiretroviral drug classes.[2]

In major randomized clinical trials (RCTs) for both first-generation and second-generation INSTIs, the development of INSTI resistance (INSTI-R) was low and almost non-existent in trials evaluating second-generation agents specifically.[3–12] However, these results only reveal resistance rates in an ideal, controlled setting, as opposed to pragmatic, real-world data. A recent analysis based on national surveillance data reported estimated INSTI-R in the USA to be 6.3%.[13] However, virological suppression and prevalence of drug resistance mutations (DRMs) are not uniform across the country.[14]

In 2016, it was estimated that only 48% of persons living with HIV (PLWH) in Chicago, IL, USA, had virological suppression at least 1 year after diagnosis.[15] Virological suppression typically occurs within the first 24 weeks after

initiation of antiretroviral therapy (ART) but is dependent upon regimen selection, medication adherence and lack of DRMs against the agents used. Known risk factors for ART non-adherence are female sex, non-white race, low education, poverty and unemployment.[16] Predictors for the development of DRMs include high pre-treatment viral loads (≥100,000 copies/mL), female sex and poor medication adherence.[17] Finally, an observational study identified age ≥40 years, injection drug use and resistance to other antiretroviral classes to be associated with INSTI-R specifically.[18]

Limited data reporting real-world incidence of INSTI-R are available because the approval and recommendation for first-line treatment with INSTIs in the 2017 US DHHS Guidelines (HIVinfo, personal communication, 2 September 2021). Increases in INSTI-R and the emergence of INSTI pan-resistant HIV are major public health concerns. HIV genotype testing and tracking prevalence of resistance may guide selection of initial ART regimens and increase the likeliness of virological suppression. The purpose of this analysis was to describe the real-world incidence of both transmitted and treatment-emergent INSTI-R in a major metropolitan area between 2017 and 2020 whilst identifying risk factors for developing INSTI-R.

Methods

Study design and population

Participants were identified via retrospective chart review from a list of PLWH with at least one clinic appointment between 2017 and 2020 generated from the University of Illinois Community Care Network (UCCN) electronic medical record. UCCN is composed of six community-based outreach clinics located in historically underserved areas of Chicago that are most affected by HIV. People were included if they were over the age of 18, initiating any new INSTI-based regimen between 1 September 2017, and 1 September 2020, followed at UCCN for at least 12 months following INSTI initiation, and had at least one HIV1 viral load collected at least 12 months after INSTI initiation. A new INSTI-based regimen could include a switch from another anchor drug class or different INSTIs. All orally available INSTI-based regimens were included as first-line recommendations, raltegravir (RAL), elvitegravir (EVG) and DTG at the beginning of the study period, and later included BIC starting in October of 2018.[1] Elite controllers, defined as individuals who are able to maintain virological suppression or a viral load of <50 copies/mL without ART, were identified from review of notes in each participant's electronic medical record and excluded from the analysis.

This study was approved by the University of Illinois Chicago Institutional Review Board (Protocol #: 2021-1210) under expedited review procedures and with waiver of informed consent due to being deemed to be no more than minimal risk in accordance with 45 CFR 46.110.

Procedures

The primary outcomes were the development of virological failure (VF) and documented INSTI-R mutation(s). VF was defined as at least two consecutive HIV1 viral loads of ≥200 copies/mL and collected at least 24 weeks after initiation of an INSTI-containing regimen. The primary endpoint was the difference in INSTI-R in the UCCN population compared with the national estimated prevalence, which was previously reported to be 6.3%.[13] Secondary endpoints included the difference in development of INSTI-R between treatment-naive and treatment-experienced persons and between first-generation and second-generation INSTIs as well as the association of person-specific factors related to medication non-adherence and the development of VF. Person-specific risk factors of interest included substance use disorders and psychiatric comorbidities as well as previously identified risk factors such as high pre-treatment viral load, female sex and non-white race.

Persons receiving HIV care at UCCN clinics during the study period were screened for inclusion. The most recent HIV1 viral load and CD4 T cell counts as well as genotypic testing collected at any time prior to initiation of an INSTI-containing regimen were considered pre-treatment. Viral loads were considered undetectable if <50 copies/mL. All laboratory values collected up to 4 years after starting INSTI-based therapy were included. In those who did not develop VF, it was assumed that they did not acquire or that they had pre-existing INSTI-R; therefore, baseline genotyping was not required for inclusion and allowed for a pragmatic study design to better reflect clinical practice. Potential risk factors for medication non-adherence, such as comorbidities and insurance coverage, were assessed when starting INSTI treatment. Additional information about participant-reported reasons for non-adherence was collected from clinic notes at the time of VF.

Statistical analysis

The primary endpoint was analysed using a χ^2 test. The secondary endpoints were analysed using logistic regression. p values of less than 0.05 were considered statistically significant. Possible predictors of VF were identified using a backward stepwise model selection with a p value threshold of 0.1 for inclusion in the final model. All statistics were run utilizing R console version 3.6.2 (Pittsburgh, PA, USA) and SAS On Demand for Academics software, Version 1 (Cary, NC, USA) of the SAS System.[19,20]

Results

A total of 948 people were screened, with 321 included in the final analysis. Reasons for exclusion are outlined in Figure 1. The average length of follow-up was 29.9 months (range: 12.1–48.0 months). Baseline characteristics are summarized in Table 1. Most participants were Black (70.1%) and male (61.4%), with a median age of 47 years. The majority had CD4+ T cell counts of >200 cells/mm^3 (87.2%) and an undetectable viral load at baseline (67.3%). A total of 158 people (49.2%) had baseline resistance testing available, of which only eight were screened for INSTI-R prior to starting an INSTI. The most common class of anchor drug prior to switching to their new regimen was first-generation INSTIs; moreover, 22 people were taking an INSTI in combination with at least one agent from another anchor drug class.

Of the 321 people included, 26 (8.1%) developed VF, and there were no known cases of acquired INSTI-R. Two of the 26 (7.7%) received subsequent INSTI-R testing, and 14 eventually achieved virological suppression without regimen changes (53.8%). Seven (26.9%) people were no longer taking ART for at least 6 weeks at the time of study-defined VF due to non-adherence to medications or to medical care in general. One person developed NRTI resistance, namely L74I, which confers intermediate-level resistance to abacavir.[21] All persons with INSTI-R included in this study had documented INSTI DRMs at study entry. Of the eight people with prior INSTI-R testing, five had INSTI DRMs. Compared with the national estimate of INSTI-R prevalence of 6.3%, participants in this study had significantly less INSTI-R with an estimated prevalence of 1.6% (p<0.001).

Persons who experienced VF had similar numbers of follow-up visits compared with those without VF, on average about three visits per year. Considering substance use disorders, psychiatric comorbidities, sex, race/ethnicity, pre-treatment viral load and INSTI, the backward stepwise logistic regression model identified INSTI, race/ethnicity and viral load as possible predictors of VF. The odds of developing VF for each potential predictor of VF are summarized in Table 2.

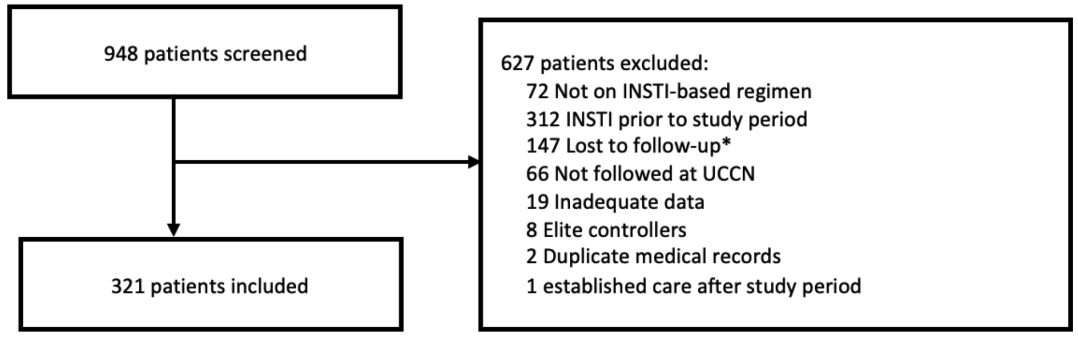
The only predictor for the development of DRMs identified in previous studies that differed significantly between persons who developed VF and the overall population in this study was high pre-treatment HIV1 RNA (OR 1.21, 95% CI 1.05–1.39).[17] A detectable pre-treatment HIV1 RNA of >50 copies/mL but <100,000 copies/mL was also associated with higher odds for development of VF (OR 1.19, 95% CI 1.11–1.27). No difference in VF was observed between persons who initiated first-generation or second-generation INSTIs. VF occurred in 2 (7.7%), 8 (30.8%), 5 (19.2%) and 11 (42.3%) people on RAL, EVG, DTG and BIC, respectively. Of the individual INSTIs, only RAL was associated with higher odds of developing VF (OR 1.55, 95% CI 1.19–2.03). A breakdown of INSTIs prescribed in this population is provided in Table 3.

Discussion

This study found similar or lower estimated rates of INSTI-R in a real-world population compared with those found in RCTs and previous observational studies (Table 4), despite a numerically higher incidence of VF.[3–12,22–41]

The discrepancy between VFs in our study and the rates identified in clinical trials may be attributed to differences in how each study defined loss to follow-up. Our study was based on less stringent inclusion and exclusion criteria compared with RCTs. People who may have been out of care for at least 12 months but returned for

Figure 1. Study profile.



*lost to follow-up: no subsequent laboratory values collected at any time > 1 year from initiation of INSTI-containing regimen

INSTI, integrase strand transfer inhibitor; UCCN, University of Illinois at Chicago Hospital and Health Sciences System Community Clinic Network.

Table 1. Baseline characteristics.

Characteristic	*n* (%)
Age, years, median (IQR)	47 (35–56)
Sex	
Male	197 (61.4)
Female	117 (36.4)
Transgender (MTF)	7 (2.2)
Ethnicity	
Black/African American	225 (70.1)
White	26 (8.1)
Hispanic/Latinx	51 (15.9)
Asian	2 (0.6)
Native American	1 (0.3)
Multiracial	4 (1.2)
Other	12 (3.7)
Undetectable viral load at baseline[a]	216 (67.3)
High viral load (>100,000 copies/mL) at INSTI initiation	16 (4.9)
$CD4^+$ T cell count, cells/mm^3, mean (SD)	555 (336)
$CD4^+$ <200 cells/mm^3, *n* (%)	41 (12.8)
Previous ART regimen anchor	
INSTI (alone)	124 (38.6)
NNRTI (naïve)	77 (23.9)
PI (alone)	60 (18.6)
Naive	35 (10.9)
Fusion inhibitor	1 (0.3)
INSTI + NNRTI	6 (1.9)
INSTI + PI	14 (4.4)
INSTI + PI + NNRTI	2 (0.6)
PI + NNRTI	1 (0.3)
PI + fusion inhibitor	1 (0.3)
Documented DRMs	
INSTI	5 (1.6)
NRTI	81 (25.2)
NNRTI	77 (23.9)
PI	43 (13.4)

[a]HIV1 RNA viral load <50 copies/mL.
ART, antiretroviral therapy; DRMS, drug resistance mutations; INSTI, integrase strand transfer inhibitor; IQR, inner quartile range; MTF, male-to-female; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SD, standard deviation.

Table 2. Potential predictors of VF (*n*=321).

Risk factor, *n* (%)	Sample (*n*=295)	VF (*n*=26)	Odds ratio (95% CI)
Sex			
Male[a]	183	14	–
Female	105	12	1.03 (0.97–1.10)
Transgender (MTF)	7	0	0.93 (0.76–1.14)
Race/Ethnicity			
Black/African American	205	21	1.02 (0.33–3.09)
White[a]	24	2	–
Hispanic/Latinx	48	3	0.98 (0.87–1.12)
Asian	2	0	0.93 (0.63–1.38)
Multiracial	4	0	0.93 (0.54–1.61)
Other/Unknown	13	0	0.93 (0.78–1.11)
Substance use	92	8	0.98 (0.41–2.33)
Psychiatric disorders	105	6	0.54 (0.21–1.39)
Pre-treatment viral load			
<50 copies/mL[a]	211	5	–
50–100,000 copies/mL	72	18	1.19 (1.11–1.27)
>100,000	12	3	1.21 (1.05–1.39)
First-generation INSTI	71	10	0.45 (0.20–1.05)
Treatment experienced	260	22	0.78 (0.26–2.33)

[a]Reference group.
INSTI, integrase strand transfer inhibitor; MTF, male-to-female; VF, virological failure.

Table 3. Odds of VF by individual INSTI.

INSTI, *n* (%)	Total sample (*n*=321)	VF (*n*=26)	Odds ratio (95% CI)
Raltegravir	4 (1.2)	2 (7.7)	1.55 (1.19–2.03)
Elvitegravir	67 (20.9)	8 (30.8)	1.06 (0.98–1.14)
Dolutegravir	70 (21.8)	5 (19.2)	1.01 (0.94–1.09)
Bictegravir[a]	180 (56.1)	11 (42.3)	–

[a]Reference group
INSTI, integrase strand transfer inhibitor; VF, virological failure.

HIV1 viral load testing at any time within 4 years after initiation of their INSTI-containing regimen regardless of whether they were still taking ART were included in this study. Therefore, it would be expected that those who re-engaged in care during the study period would have detectable viral loads when restarting ART and may fall under this study's definition of VF.

The number of people with interruptions in ART was not collected. At study entry, about one-third of all people had a detectable viral load with only 10.9% of those entering the study being treatment naive. The discordance

Table 4. INSTI-resistance rates.

Integrase inhibitor	Study (year)		Baseline resistance		Virological failure, n/N (%)	Development of INSTI-resistance mutation, n/N (%)
			INSTI *n/N* (%)	NRTI *n/N* (%)		
Randomized controlled trials						
RAL	STARTMRK (ref.[3]) (2013)[a]		–	–	55/281 (19.6)	4/281 (1.4)
	BENCHMRK (ref.[4]) (2013)		–	–	166/462 (35.9)	89/462 (19.2)
	SWITCHMRK 1–2 (ref.[5]) (2010)		–	–	32/350 (9.1)	9/350 (2.5)
EVG	Study 102 (ref.[6]) (2012)[a]		–	–	14/353 (4.0)	8/353 (2.3)
	Study 103 (ref.[7]) (2012)[a]		–	–	12/357 (3.4)	4/357 (1.1)
RAL, DTG	SPRING-2 (ref.[8]) (2013)[a]	RAL	20/332 (6.0)	4/332 (1.2)	29/332 (8.7)	1/332 (0.3)
		DTG	10/349 (2.9)	0/349 (0.0)	22/349 (6.3)	0/349 (0.0)
DTG	VIKING-1 (ref.[9]) (2013)[b]	DTG daily	27/27 (100.0)	–	12/27 (44.4)	5/27 (18.5)
		DTG BID	24/24 (100.0)	–	5/24 (8.3)	4/24 (16.7)
	TANGO (ref.[10]) (2020)[a]	DTG/3TC	0/322 (0.0)	4/322 (1.2)	0/322 (0.0)	0/322 (0.0)
		DTG/3TC + TAF	0/321 (0.0)	3/321 (0.9)	1/321 (0.3)	0/321 (0.0)
BIC, DTG	Study 1878 + 1844 (ref.[11]) (2018)	DTG	2/14 (14.3)	4/138 (2.9)	0/281 (0.0)	0/281 (0.0)
		BIC	87/170 (51.2)	52/405 (12.8)	0/572 (0.0)	0/572 (0.0)
	Study 1489 + 1490 (ref.[12]) (2019)[a]	DTG	322/640 (50.3)	14/640 (2.2)	5/640 (0.8)	0/640 (0.0)
		BIC	333/634 (52.5)	21/634 (3.3)	8/634 (1.3)	0/634 (0.0)
Real-world data						
RAL, EVG, DTG, BIC	**Current study**		**5/321 (1.6)**	**81/321 (25.2)**	**26/321 (8.1)**	**0/321 (0.0)**
	Lan et al. (ref.[22]) (2022)		–	–	1208/1208 (100)	32/1208 (2.65)
DTG, BIC	Parczewski et al. (ref.[23]) (2023)[c]		–	–	51/610 (8.3)	1/719 (0.1)
RAL, EVG, DTG	Kamori et al. (ref.[24]) (2023)[c]		–	–	137/137 (100)	8/137 (5.8)
	Lepik et al. (ref.[25]) (2017)		4/985 (0.4)	76/985 (7.7)	210/985 (21.3)	14/985 (1.4)
	Scutari et al. (ref.[26]) (2020)		4/107 (3.7)	NR	102/107 (95.3)	39/107 (36.4)
	Steegen et al. (ref.[27]) (2019)[c]		–	–	43/1084 (4.0)	22/1084 (2.0)
RAL, DTG	Seatla et al. (ref.[28]) (2021)[c]		–	–	34/34 (100)	11/34 (32)
RAL	De Souza Cavalcanti et al. (ref.[29]) (2014)[c]		–	–	69/69 (100)	47/69 (68)
DTG	Abdullahi et al. (ref.[30]) (2023)[c]		–	–	452/4263 (10.6)	1/4263 (<0.1)
	Armenia et al. (ref.[31]) (2023)		–	–	467/467 (100)	58/467 (12.4)
	Bowman et al. (ref.[32]) (2023)		2/561 (0.4)	0 (0.0)	6/561 (1.0)	1/561 (0.2)
	Castagna et al. (ref.[33]) (2018)		117/142 (82)	96/142 (68)	48/142 (33.8)	9/142 (6.3)
	COPEDOL (ref.[34]) (2022)		9/440 (2.0)	NR	17/440 (3.9)	14/440 (3.2)
	Deschanvres et al. (ref.[35]) (2021)		0 (0.0)	1/1374 (<0.1)	45/1374 (3.3)	2/1374 (0.1)
	Diaz et al. (ref.[36]) (2023)[c]		–	–	113/113 (100)	25/113 (22.1)
	DTG RESIST (ref.[37]) (2023)		–	–	599/599 (100)	36/599 (6.0)
	Gil et al. (ref.[38]) (2022)		–	–	2696/2696 (100)	174/2696 (6.5)
	Palmier et al. (ref.[39]) (2023)		0 (0.0)	17/358 (5.0)	13/358 (4.0)	1/358 (0.3)
	Schramm et al. (ref.[40]) (2022)[c]		0 (0.0)	53/1838 (2.8)	14/1838 (0.8)	2/1838 (0.1)

(*Continued*)

Table 4. (Continued)

Integrase inhibitor	Study (year)	Baseline resistance		Virological failure, n/N (%)	Development of INSTI-resistance mutation, n/N (%)
		INSTI *n/N* (%)	NRTI *n/N* (%)		
BIC	Nasreddine et al. (ref.[41]) (2023)	–	–	14/2001 (0.7)	1/2001 (<0.1)

[a] Treatment naive individuals.
[b] All patients were failing therapy at baseline, this represents non-response to regimen switch.
[c] Conducted in resource-limited settings.
3TC, lamivudine; BIC, bictegravir; BID, twice daily; DTG, dolutegravir; EVG, elvitegravir; INSTI, integrase strand transfer inhibitor; NR: not reported; NRTI, nucleoside reverse transcriptase inhibitor; RAL, raltegravir; TAF, tenofovir alafenamide.

between these two proportions may be due to people re-engaging in care at the time of study entry. A detectable HIV1 RNA viral load, defined as >50 copies/mL, was associated with higher odds of developing VF, which may be a result of individuals coming in and out of care throughout the study period.

In contrast to low rates of VF in RCTs, BIC was the most common INSTI in this population who experienced study-defined VF, and RAL was the least common. This likely reflects trends in prescribing during the study period of which the majority took place following the approval and subsequent first-line recommendation of coformulated BIC, emtricitabine and tenofovir alafenamide in 2018. Moreover, RAL was the only INSTI associated with higher odds of VF in this study. There are several possible explanations for this observation. RAL was the first INSTI to be approved by the FDA in 2007, not to be followed by a second INSTI, EVG, until 2012.[42,43] Upon approval, RAL was reserved for salvage therapy in treatment-experienced PLWH.[42] These individuals may not have had many fully active agents remaining to take concomitantly with RAL. Additionally, RAL required twice-daily dosing until the approval of the high-dose formulation in 2017, which may have led to decreased adherence due to increased pill burden.[42,44] Finally, RAL is a first-generation INSTI and, therefore, has a lower barrier to resistance, or lower number of DRMs necessary to confer resistance to RAL, than its second-generation counterparts.[8,45]

Lower rates of VF in our study compared with RCTs and the national prevalence estimate may be due to the higher utilization of second-generation INSTIs with higher barriers to resistance and decreased pill burden in the study population.

Limitations

Limitations of this study included its retrospective nature; therefore, investigators had a limited number of genotypes available to them both from prior to initiating an INSTI and at the time of VF. The low number of INSTI-R tests performed may be due to a lack of guideline recommendation to do so prior to initiating ART.[1] Moreover, the recommendation to obtain a genotype of the reverse transcriptase and protease regions prior to starting ART was not made by the DHHS until May of 2006, later than some participants may have initiated ART. There is still no recommendation to obtain genotyping of the INSTI region due to low prevalence of INSTI resistance in the USA. Whilst it was assumed that patients who did not develop VF did not have or developed INSTI-R, it is possible that they could have baseline EVG or RAL resistance with residual susceptibility to second-generation agents that would not be accounted for.[45] However, given the observational nature of this study, it reflects the prevalence of resistance that would be detected in clinical practice as did the national estimate used as a comparator, which was generated from routine sequence data from local health departments and reported to the US National HIV Surveillance System.[12] People with baseline INSTI-R may have been excluded from the study due to either being switched to a non-INSTI-containing regimen or not switching regimens during the study period at all. Finally, power was not calculated due to the scarcity of pre-existing data for non-RAL INSTI-R.

Some strengths of the study were the inclusion of a diverse population, both from a racial and gender perspective, and from multiple clinic locations across the city of Chicago. Because this study was observational, it is reflective of real-world development of resistance due to being conducted outside of the confines of stringent RCT protocols. Additionally, there was a long duration of follow-up with data available on average for about 30 months after INSTI initiation.

Conclusion

In conclusion, the true rate of INSTI-R amongst people receiving care within UCCN is still unknown. Amongst those who switched to INSTI-containing regimen between 2017 and 2020, estimated INSTI-R rates are lower than national prevalence estimates.

Contributions: JJ: conceptualization, methodology, formal analysis, writing – original draft, review and editing. ED: conceptualization, methodology, writing – review and editing. RB and RS: writing – review and editing. MB: conceptualization, methodology, writing – review and editing, supervision. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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