

https://dspace.org/

Frequency of tuberculosis symptoms at repeat visits amongst adults attending for HIV care in Gauteng province South Africa

Thobani Ntshiqa; S Jawad; Y Hanifa; Violet Chihota; Salome Charalambous ...

https://hdl.handle.net/10539/48221
WOS

Downloaded from a DSpace repository. https://dspace.org/

BMC Public Health

RESEARCH

Open Access

Frequency of tuberculosis symptoms at repeat visits amongst adults attending for HIV care in Gauteng province, South Africa

Thobani Ntshiqa[1,3*], Sena Jawad[2], Yasmeen Hanifa[2], Violet Chihota[1,3,5], Salome Charalambous[1,3,5], Nontobeko Ndlovu[1], Gavin Churchyard[1,3,5], Katherine Fielding[2,3†] and Alison D. Grant[2,4†]

Abstract

Background Intensified tuberculosis (TB) case finding is recommended for people living with HIV (PLHIV) at every clinical encounter using the World Health Organization (WHO) screening tool (W4SS), comprising any of current cough, fever, night sweats or weight loss. We determined the frequency of W4SS symptoms at repeat visits among individuals without TB attending for HIV care in Gauteng province, South Africa.

Methods In a cohort study, we enrolled PLHIV (adults) attending clinics for routine HIV care. At enrolment, patients were screened using W4SS, and categorised into high (cough, body mass index (BMI) ≤ 18.5, CD4 < 100 cells/mm^3, fever ≥ 3 weeks, and unintentional weight loss ≥ 10%), medium (1 ≥ W4SS symptoms but not fulfilling criteria for high priority) or low priority (no W4SS symptoms) for TB testing with Xpert MTB/RIF; and anyone diagnosed with TB was excluded. This analysis was restricted to individuals with no TB diagnosis by month three.

Results We enrolled 3,738 patients in the parent study. Of this, 88.5% (3,309/3,738) completed month three follow up visits, of whom 71.0% (2,349/3,309) were female, median CD4 count 427 [interquartile range (IQR) 275–607] cells/mm^3, 71.8% (2,377/3,309) on antiretroviral therapy (ART) with median duration 4 [IQR 2–7] years). At enrolment, 29.9% (991/3,309) were positive on W4SS, among whom 62.7% (621/991) were pre-ART. The proportion of patients who reported any of the four symptoms on W4SS was 15.1% (331/2,191) at month one, 13.5% (276/2,052) at month two, and 8.9% (294/3,309) at month three. Cough was the symptom most frequently reported at all time points, followed by weight loss and then night sweats.

Conclusion W4SS symptoms remained relatively common at repeat visits among people without TB in HIV care. Repeat testing of symptomatic patients with Xpert MTB/RIF would have substantial resource implications. Sensitive and specific TB screening tools which are not dependent on symptoms are needed.

Keywords TB case finding, W4SS symptom screening, PLHIV, Xpert MTB/RIF, South africa

†Katherine Fielding and Alison D. Grant contributed equally to this work.

*Correspondence:
Thobani Ntshiqa
tntshiqa@auruminstitute.org
[1]The Aurum Institute, Johannesburg, South Africa
[2]TB Centre, London School of Hygiene & Tropical Medicine, London, United Kingdom
[3]School of Public Health, University of the Witwatersrand, Johannesburg, South Africa
[4]Africa Health Research Institute, School of Laboratory Medicine & Medical Sciences, College of Health Sciences, University of KwaZulu-Natal, Durban, South Africa
[5]Department of Medicine, Vanderbilt University, Nashville, TN, USA

© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

Introduction

In 2021, South Africa was one of the eight counties with the largest number of incident tuberculosis (TB) episodes, with more than half of the TB episodes among people living with HIV (PLHIV) [1]. The risk of acquiring TB is 14 times higher among PLHIV than HIV-negative individuals in the same country [2]. The World Health Organization (WHO) recommends TB screening at every clinical encounter for PLHIV in areas with a high prevalence of TB [3]. The recommendations include the use of the WHO TB screening tool (W4SS), defined as reporting any cough, fever, night sweats or unintentional weight loss [3, 4]. The tool is intended for use to rule out TB; those reporting no symptoms should start TB preventive therapy (TPT) if there are no contraindications. Those reporting at least one symptom should be investigated further for TB.

In 2011, the South African Department of Health implemented Xpert MTB/RIF as the primary test for diagnosing TB, replacing two sputum smears [5, 6]. Under these guidelines, clinic attendees reporting one or more symptoms from the screening tool undergo an immediate Xpert MTB/RIF test. The WHO screening tool aims to maximise sensitivity and negative predictive value, resulting in low specificity and positive predictive value [7]. Consequently, only a small fraction of those who present with symptoms will genuinely have TB, yet under the current guidelines all should have the relatively costly Xpert MTB/RIF test.

Little is known about the natural history of W4SS symptoms among PLHIV attending clinic. If a report of any W4SS symptom at any visit triggered an Xpert MTB/RIF test, demand for Xpert MTB/RIF tests would be very high. Persistent symptoms suggest a need for further investigation, while temporary symptoms indicate the need to improve the specificity of the screening tool. Understanding the natural history of TB symptoms among PLHIV is essential to optimize use of Xpert MTB/RIF testing for improved risk stratification, particularly in high-burden, resource-limited settings to ensure that PLHIV with persistence TB symptoms are prioritized for diagnostic testing. Data on persistent TB symptom may be used to inform timing of TB testing and support refinement of screening algorithms. Incorporating information on symptom duration into TB screening strategies can improve specificity, reduce costs, and guide more nuanced clinical decisions. This approach may offer an important means of balancing early TB detection with the operational and financial constraints faced by TB programs in low-resource settings.

The XPHACTOR study (Xpert for people attending HIV/AIDS care: test or review) evaluated a diagnostic algorithm among PLHIV attending clinic in Gauteng province, South Africa [8–10]. The algorithm prioritised immediate testing with Xpert MTB/RIF for those at highest risk of TB mortality or transmission while deferring investigation for those at lower risk to help reduce health service costs with minimal risk to patients.

Using data from the XPHACTOR study, we described the natural history of self-reported W4SS symptoms among PLHIV attending clinic without a diagnosis of TB by three months after enrolment. We also reported on seasonal variation for self-reported cough and fever to investigate if these symptoms were more common in the influenza season.

Materials and methods

Design of parent study

The XPHACTOR study was a prospective cohort study conducted in Gauteng province, South Africa, between September 2012 and March 2014, when Xpert MTB/RIF was being rolled out. Clinic attendees were recruited from four public sector clinics (two hospital-based, two community health centres) providing HIV care. Clinics were selected for the study if they had a total active population of at least 500 PLHIV and, at the time of the study, were not routinely testing sputum with Xpert MTB/RIF. At the time of the study, ART eligibility comprised CD4 ≤ 350 cells/mm^3 or WHO clinical stage ≥ 3.

Patient selection criteria and follow-up for the parent study

Consecutive eligible, consenting adult patients attending for HIV care, between September 2012 and March 2014, were included in the study regardless of whether or not they reported symptoms suggestive of TB. Patients were excluded if they were on TB treatment, completed treatment in the last three months or needed urgent referral to a higher level of care. At enrolment, patients reporting at least one of cough, fever of ≥ 3 weeks, drenching night sweats or measured weight loss ≥ 10%, or with body mass index (BMI) ≤ 18.5 kg/m^2 or CD4 < 100 × 10^6/l, provided a sputum specimen for an immediate Xpert MTB/RIF. At follow up, if the Xpert MTB/RIF result was negative, a chest radiograph, another symptom screen and further investigations for TB were carried out. For study purposes, all patients had sputum taken at enrolment which was processed after three months using Xpert MTB/RIF to verify the absence of active TB at enrolment.

Patients who were symptomatic and/or not on ART at enrolment were asked to attend for follow-up visits at month one and two for repeat W4SS symptom screen. All patients were invited for a face-to-face interview at three months where W4SS symptoms were ascertained, and sputum (induced if necessary) and blood were collected for mycobacterial culture. Patients who gave sputum for testing with Xpert MTB/RIF at baseline had a repeat Xpert MTB/RIF test at three months. Further

details about methods used in parent study are described elsewhere [8].

Study sample for current analysis

For this analysis, we restricted the XPHACTOR study cohort to patients who had been followed to three months with sputum taken at three months, and who had symptom data available at enrolment and three-month visits. The National Institute for Communicable Diseases (NICD) in South Africa provided data on influenza-like-illness reported through their sentinel surveillance [11].

Statistical methods

Demographic variables were summarised by the median and interquartile range (IQR) for quantitative data and percentages for categorical data. The number of symptoms reported, and frequency of specific symptoms were summarised at each study visit. Positive for the W4SS screening tool was defined as any of cough, fever, night sweats or unintentional weight loss. We classified patients into groups defined by a within-participant comparison of symptoms reported at enrolment and three months: asymptomatic at both time points; symptomatic at both time points; change from asymptomatic at enrolment to symptomatic at three months; or symptomatic at enrolment to asymptomatic at three months. Persistent symptoms were defined as presenting with the same symptom at enrolment and at the three months visit.

Results

Participants screening and enrolment

The parent study recruited 3,738 patients of whom 88.5% (3,309/3,738) fulfilled the criteria for this analysis (Fig. 1).

Baseline characteristics

Of these patients, 71.4% (2,361/3,309) were female with the median age of 39.6 years (interquartile range [IQR] 37–41 years) and median CD4 count 427 cells/mm^3 (IQR 275–607 cells/mm^3). Overall, 71.8% (2,377/3,309) were on ART, with a median duration on treatment of 4 years (IQR 2–7 years). The median age for those on ART and pre-ART was 41 (35.6—47.9) and 34 (28.8—41.4) years respectively ($p = 0.043$) (Table 1). Previous TB disease was more common in the on-ART group (39.2%, 931/2,377) compared with the pre-ART group (7.3%, 68/932, $p < 0.001$).

Frequency of TB symptom at enrolment and follow up visits

At enrolment, 29.9% (991/3,309) were positive on the W4SS screening tool (Table 2). The most common symptom was cough (18.5%, 613/3,309), followed by unintentional weight loss (12.1%, 400/3,309), night sweats (7.0%, 233/3,309) then fever (5.1%, 168/3,309). The majority (69.4%, 688/991) of symptomatic patients reported a single symptom. When a combination of symptoms was reported, cough was most commonly reported (Table 2). During follow-up, 15.1% (331/2,191) patients were symptomatic at month one, 13.5% (276/2,052) at month two and 8.9% (294/3,309) at month three with majority of patients reporting at least one symptom (Table 2). At three months, cough remained the most frequent symptom (5.5%, 183/3,309) followed by weight loss (3.2%, 106/3,309).

Symptom status at baseline and 3-month follow up visit

Overall, 4.5% (148/3,309) of patients reported any symptom at both the enrolment and three-month visit (Table 3), with 14.9% (148/991) presenting any symptom at enrolment continuing to present a symptom at the three months visit. Patients reporting persistent symptoms were a minority; 10.0% (61/613) of those who reported cough at enrolment reported the symptom again at three months. Some patients continued to report the same symptom at three months as measured at baseline and most (25.5%, 843/3,309) patients who changed their symptom status went from symptomatic at enrolment to asymptomatic at three months (Table 3).

Seasonal variation of TB symptoms

The percentage of patients reporting cough or fever were high in September (33.1% and 22.4%, respectively) and October (31.0% and 12.2%, respectively). Surveillance data show that the number of people reporting influenza-like-illness peaked in June 2013. However, there was no clear seasonal variation in the proportion of participants reporting cough or fever and no evidence that these symptoms were more common during the South African influenza season (Fig. 2).

Discussion

This analysis shows that slightly more than a quarter of adults without active TB attending South African clinics for HIV care reported one or more symptoms from the W4SS at study enrolment. The frequency of TB symptoms reported in this study is comparatively similar to the frequency reported in baseline results from a clinical trial conducted at the outpatient clinics in South Africa and Kenya among PLHIV who were not on ART [12]. However, the frequency of TB symptoms reported in this study was slightly higher compared to frequencies reported among pre-ART and on ART patients attending HIV care in Khayelitsha township [13] and among the unknown, HIV-negative and PLHIV attending primary healthcare in Diepsloot township [14]. Several factors could account for the differences in reported symptom frequences between studies including differences in immunological statuses [low CD4 cell count

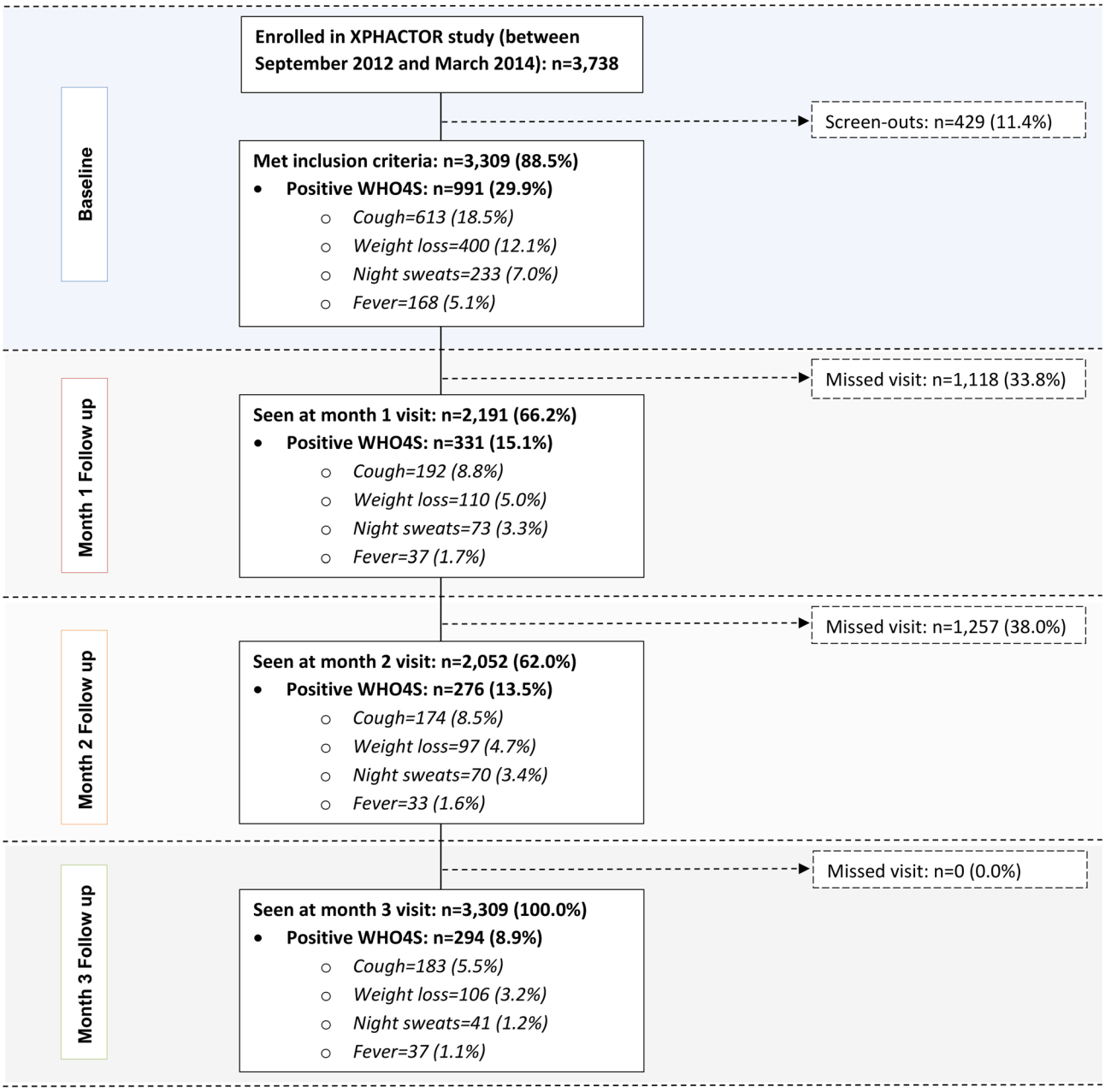


Fig. 1 Participants flow chart at enrolment

[15], profound immunosuppression [16], high viral load [17], clinical characteristics [recent ART status [18, 19], type of TB disease [20], malnutrition, co-infections and comorbidities such diabetes [21, 22], TB treatment history and drug resistance [23], and socio-demographic factors [behavioural factors such as smoking and alcohol use [24], demographic variables such as age and sex [25, 26]. Understanding these factors is essential for developing effective screening strategies and diagnostic tools tailored to PLHIV. Although there were variations in the reported frequencies of TB symptoms, most studies reported very low TB prevalence ranging from 2% [14] to 5% [12].

Fewer patients reported symptoms at subsequent monthly visits, but nearly 9% reported at least one symptom at three months. If all PLHIV people had a symptom screen at each clinic visit and those reporting any symptom underwent testing with Xpert MTB/RIF, this would generate a massive and costly volume of tests. As a more general example, it is estimated that if Xpert MTB/RIF was used for 15% of TB suspects in India, it would consume the entire annual budget of the TB programme [27]. A multi-national study in Thailand, Cambodia and

Table 1 Baseline characteristics of the cohort (*n* = 3,309)

		All Patients (*n*=3,309)	On-ART (*n*=2,377)	Pre-ART (*n*=932)
Age (Years)				
Median (IQR)		39.6 (33.2, 46.5)	41.3 (35.6, 47.9)	34.1 (28.8, 41.4)
Minimum, Maximum		18.7, 82.8	19.9, 82.8	18.7, 71.5
Sex				
Female	*N* (%)	2,361 (71.4)	1,694 (71.3)	667 (71.6)
Previous TB disease				
Yes	*N* (%)	999 (30.2)	931 (39.2)	68 (7.3)
Duration on ART (Years)[1]				
Median (IQR)		4.1 (2.3, 6.6)	4.1 (2.3, 6.6)	-
Minimum, Maximum		0, 21.0	0, 21.0	
CD4 Count (cells/μl)[2]				
Median (IQR)		427 (275, 607)	434 (278, 619)	416 (264, 562)
Minimum, Maximum		2, 1,644	2, 1,577	3, 1,644

[1]Duration on ART: missing 10 on ART

[2]CD4: missing 8 on-ART, 129 pre-ART

Table 2 Follow up results of the cohort (*n* = 3,309)

	At enrolment	1 month	2 months	3 months
N	3,309	2,191	2,052	3,309
Number of symptoms reported [% (*n*)]				
None	70.1% (2,318)	84.9% (1,860)	86.5% (1,776)	91.1% (3,015)
1 symptom	20.8% (688)	12.1% (265)	10.0% (205)	7.1% (235)
2 symptoms	6.2% (205)	2.4% (52)	2.4% (50)	1.4% (46)
≥3 symptoms	3.0% (98)	0.6% (14)	1.0% (21)	0.4% (13)
Type of symptoms reported [% (*n*)]				
Cough	18.5% (613)	8.8% (192)	8.5% (174)	5.5% (183)
Unintentional weight loss	12.1% (400)	5.0% (110)	4.7% (97)	3.2% (106)
Night sweats	7.0% (233)	3.3% (73)	3.4% (70)	1.2% (41)
Fever	5.1% (168)	1.7% (37)	1.6% (33)	1.1% (37)
Symptom combinations[1]: [% (*n*)][2]				
N	991	331	276	294
Cough alone	36.8% (365)	42.6% (141)	42.8% (118)	44.9% (132)
Weight loss alone	20.7% (205)	21.5% (71)	21.0% (58)	26.5% (78)
Night sweats alone	8.9% (88)	11.5% (38)	7.6% (21)	5.8% (17)
Cough and weight loss	7.5% (74)	4.8% (16)	5.4% (15)	6.1% (18)
Cough and fever	5.1% (50)	3.3% (11)	1.8% (5)	5.8% (17)
Cough and night sweats	3.4% (34)	3.3% (11)	5.4% (15)	1.4% (4)
Fever alone	3.0% (30)	4.5% (15)	2.9% (8)	2.7% (8)
Cough, night sweats & weight loss	3.2% (32)	2.1% (7)	1.8% (5)	1.0% (3)
Other	11.4% (113)	6.3% (21)	11.2% (31)	5.8% (17)

[1]Of those reporting at least one symptom

Table 3 Symptom status at baseline and 3-month follow up visit

All patients (*n* = 3,309)	Any symptom	Cough	Fever	Night sweats	Weight loss
No symptom at either visit	2,172 (65.6)	2,574 (77.8)	3,112 (94.1)	3,054 (92.3)	2,833 (85.6)
Asymptomatic to symptomatic	146 (4.4)	122 (3.7)	29 (0.9)	22 (0.7)	76 (2.3)
Symptomatic to asymptomatic	843 (25.5)	552 (16.7)	160 (4.8)	214 (6.5)	370 (11.2)
*Persistent symptoms	148 (4.5)	61 (1.8)	8 (0.2)	19 (0.6)	30 (0.9)

Data are frequency (%)

*Defined as presenting with the same symptom at enrolment and at the three months visit

Vietnam screened PLHIV for TB using cough, fever and night sweats and emphasised the importance of using multiple symptoms as a screening mechanism and not only cough [7].

Among our symptomatic patients, cough remained the most common symptom presented at both time points, followed by unintentional weight loss. A relatively large number of people who did not have TB disease reported symptoms. These results were consistent with findings from a multicentre clinical trial conducted in South Africa and Kenya at outpatient clinics among PLHIV who were not on ART [12]. The W4SS symptom questionnaire was designed to maximise sensitivity rather than specificity [28] and, accordingly, asks patients if they had noticed a cough within the last 24 h rather than prolonged cough. Therefore, the lack of specificity is not surprising. Using any one symptom prioritizes sensitivity, although it also leads to low specificity and high number of tests per TB case detected [29]. Previous studies have shown that requiring ≥ 2 symptoms improves specificity while only modestly reducing sensitivity [30]. This trade-off may lead to fewer tests and lower costs without significantly increasing missed cases. Algorithms combining symptom severity, duration, and number are more predictive than single symptoms [31]. Modelling studies demonstrate that restricting Xpert MTB/RIF to patients with ≥ 2 symptoms or high-risk profiles can reduce test volume and costs by up to 30–40%, with only a minor impact on TB case detection [32]. Using combinations of TB symptoms rather than any symptom alone among PLHIV can reduce the number of Xpert MTB/RIF tests performed and thereby lower costs in TB screening programs. Self-reported W4SS symptoms were more prevalent among patients attending pre-ART care than ART care at the enrolment visit, although more ART than

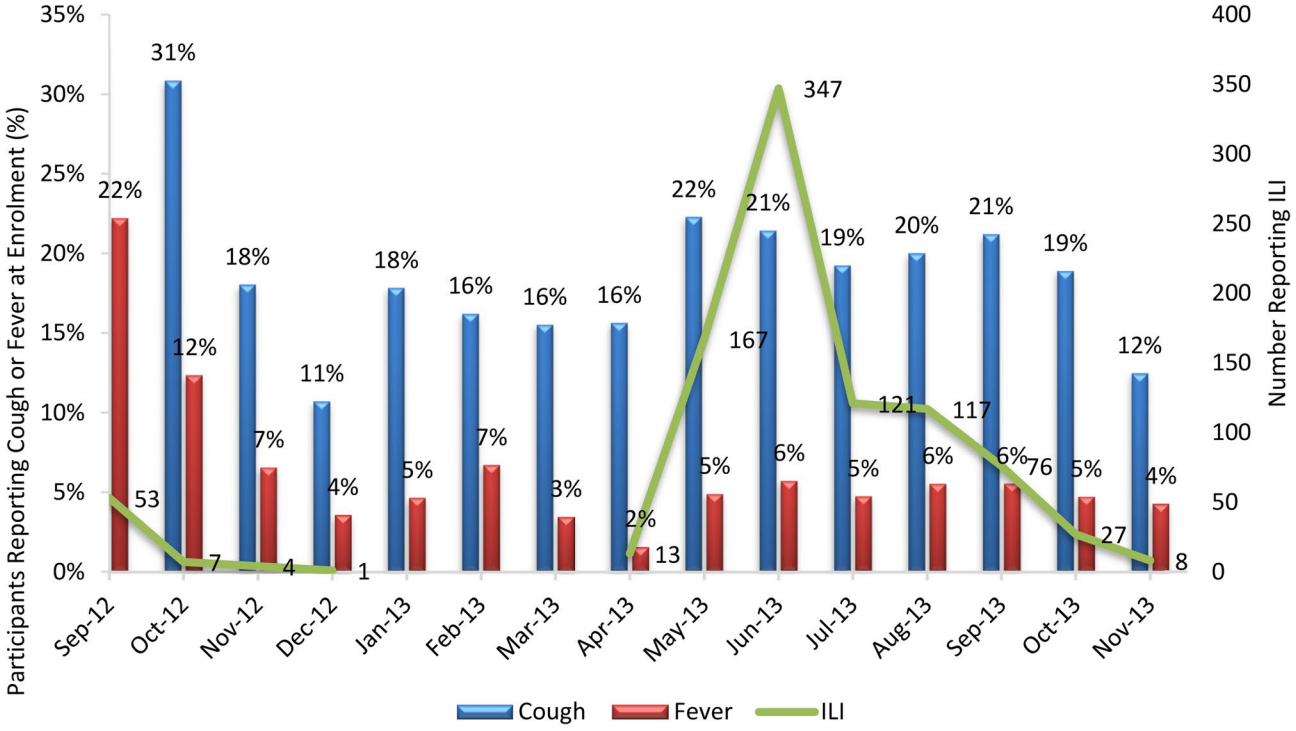


Fig. 2 Proportion of patients reporting cough and fever at study enrolment, and South African surveillance data showing number reporting influenza-like illness, by calendar month

pre-ART patients reported at least one TB symptom over time. ART is known to protect against HIV-related diseases and increase CD4 cell count [33]. In a cross sectional study conducted in one of the Cape Town townships, Rangaka et al. also found that pre-ART patients were four times more likely to report W4SS symptoms compared to those on ART with WHO screening tool correctly identifying 64% of those who truly have TB in pre-ART group while identifying 59% among those on ART [34]. This may suggest that WHO symptom screen alone may be less reliable to rule out TB disease among PLHIV on ART [35], as illustrated by the fact that most patients with culture-confirmed TB in the Cape Town cohort had none of the four TB symptom suggested in the WHO screening tool [34].

Despite widespread use of the W4SS for TB screening in PLHIV, its low specificity has led to high rates of unnecessary confirmatory testing, often with limited diagnostic yield and increased cost. As a result, there is growing interest in augmenting symptom-based screening with additional triage tools to improve diagnostic efficiency while preserving sensitivity. One promising addition is C-reactive protein (CRP), a non-specific inflammatory biomarker that is elevated in active TB disease. A meta-analysis showed that CRP (using a threshold of ≥ 5 mg/L) had a sensitivity of 87% and specificity of 67% for active TB [36]. This performance is comparable to or better than the W4SS, especially among outpatients and ART-naïve individuals. CRP offers several practical advantages including point-of-care availability, operational feasibility, and improved specificity. Incorporating CRP into TB screening strategies for PLHIV represents a promising innovation to overcome the limitations of symptom-based screening alone.

Unlike previous studies [37, 38], our data did not show any clear increase in the frequency of cough and fever during South Africa's influenza season (i.e. May-September), suggesting that when PLHIV report these symptoms they should not be assumed to be attributable to influenza. However, the difference may be due to geographic locations of the four clinics in our study, limited sample size or an unusual 2013 flu season.

Limitations

In order to interpret the data transparently, all missing symptom data at enrolment and the three-month visit were deleted from the analysis which limited using all the observations from the parent XPHACTOR study. Some patients were not able to attend the three months visit and instead were given a telephonic interview, yet a sputum sample could not have been taken and unless the participant was re-admitted to hospital following the telephone interview, it was not possible to rule out TB for these few. The main limitation of this study is that the data were collected from 2012 to 2014 at a time when guidelines were different. The main difference was that

ART was only started when people met specific criteria i.e., a CD4 count ≤ 350 cells/mm^3 or WHO clinical stage ≥ 3 [39]. The population included in this study therefore probably had a lower median CD4 cell count than we would expect among PLHIV attending clinic at present. Thus, they may have been more immunosuppressed and more likely to report symptoms than clinic attendees in more recent times. Another difference is that at the time of the study, many people taking ART were attending clinic monthly to collect ART and our study was designed assuming that they would undergo a symptom screen at every monthly visit. Current guidelines [40] aim to reduce the frequency of clinic visits for people taking ART who are well; however, in practice, many patients continue to make monthly visits to collect ART [41, 42] and our study is relevant to them.

Conclusion

W4SS symptoms were common among adult HIV clinic attendees who did not have TB. Symptoms were less common at subsequent monthly visits but even at the three-month visit, 9% patients reported one symptom. Cough and fever were not more commonly reported during the influenza season. Testing all W4SS symptomatic individuals with Xpert MTB/RIF would generate a very large number of unnecessary negative tests. Better TB diagnostic tests which are not dependent on symptoms are needed for primary healthcare clinics. The proportion of patients testing positive on W4SS screening was three times lower at month three follow up visits compared to enrolment visits, suggesting a likely decline in the demand for a repeat Xpert MTB/RIF at follow up visit in this population group.

Abbreviations

ART	Antiretroviral therapy
BMI	Body mass index
HIV	Human immunodeficiency virus
IQR	Interquartile range
PLHIV	People living with HIV
NICD	National Institute for Communicable Diseases
TB	Tuberculosis
TPT	TB preventive therapy
WHO	World Health Organization
W4SS	World Health Organization screening tool
XPHACTOR	Xpert for people attending HIV/AIDS care: test or review

Acknowledgements

The authors would like to thank the study participants; the nursing and medical staff of Chris Hani Baragwanath (Johannesburg) and Mamelodi Hospitals (Pretoria), Ramokonopi (Ekurhuleni) and Jabulani Dumane (Ekurhuleni) community health clinics, South Africa; the staff of National Health Laboratory Services; and the staff ofAurum Institute, Johannesburg, South Africa, for their essential contributions to this study. We gratefully acknowledge funding from the Bill and Melinda Gates Foundation, Seattle, WA, USA (OPP1034523). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Authors' contributions

Conceived and designed the experiments: SJ, YH, VC, SC, GC, KF, ADG. Performed the experiments: TN, SJ, YH, VC, SC, NN, GC, KF, ADG. Analysed the data: YH, KF, ADG. Wrote the paper: TN, SJ, YH, VC, SC, NN, GC, KF, ADG.

Funding

This study was funded by the Bill & Melinda Gates Foundation [OPP1034523]. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Data availability

All data underlying the results are available as part of the article and no additional source data are required. Raw data is available upon request under custom data sharing agreement and will require authorization from Principal Investigators (Professor Violet Chihota [VChihota@auruminstitute.org], Professor Katherine Fielding [Katherine.Fielding@lshtm.ac.uk], and Professor Alison D. Grant [Alison.Grant@lshtm.ac.uk]).

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committees at the University of the Witwatersrand, University of Cape Town, and the London School of Hygiene & Tropical Medicine. All consenting participants gave written consent or, for illiterate participants, witnessed verbal consent. For illiterate participants, there was an impartial witness present during the consenting process, who then signed the relevant witness section of the consent form. All ethics committees approved the consent form, including the section on the use of witnessed oral consent for illiterate participants, at the beginning of the study. Principles expressed in the Declaration of Helsinki were followed in the conduct of this research.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 21 August 2024 / Accepted: 18 September 2025
Published online: 29 October 2025

References

1. WHO. Global tuberculosis report 2021. Geneva: World Health Organization. 2021. Licence: CC BY-NC-SA 3.0 IGO. 2021. Available from: https://www.who.int/publications-detail-redirect/9789240037021. Cited 10 Feb 2023.
2. WHO. Global tuberculosis report 2023. Geneva: World Health Organization. 2023. Licence: CC BY-NC-SA 3.0 IGO. 2023. Available from: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023. Cited 7 Jan 2024.
3. World Health Organisation. Systematic screening for active tuberculosis: principles and recommendations. World Health Organization; 2013. https://books.google.co.za/books?id=g7EXDAAAQBAJ
4. Uplekar M, Creswell J, Ottmani SE, Weil D, Sahu S, Lönnroth K. Programmatic approaches to screening for active tuberculosis. Int J Tuberc Lung Dis. 2013;17(10):1248–56.
5. World Health Organization. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children: policy update. World Health Organization. 2013. xv, 79 p. Available from: https://apps.who.int/iris/handle/10665/112472. Cited 10 Feb 2023.
6. National Tuberculosis Management Guidelines. 2014. Available from: https://www.tbonline.info/media/uploads/documents/national_tuberculosis_management_guidelines_%282014%29.pdf. Cited 10 Feb 2023.
7. Cain KP, McCarthy KD, Heilig CM, Monkongdee P, Tasaneeyapan T, Kanara N et al. An Algorithm for Tuberculosis Screening and Diagnosis in People with HIV. N Engl J Med. 2010;362(8):707–16. Available from: https://doi.org/10.1056/NEJMoa0907488. Cited 12 Apr 2021.

8. Hanifa Y, Fielding KL, Chihota VN, Adonis L, Charalambous S, Foster N et al. A clinical scoring system to prioritise investigation for tuberculosis among adults attending HIV clinics in South Africa. PLOS ONE. 2017;12(8):e0181519. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0181519. Cited 10 Feb 2023.
9. Hanifa Y, Silva ST, Karstaedt A, Sahid F, Charalambous S, Chihota VN et al. What causes symptoms suggestive of tuberculosis in HIV-positive people with negative initial investigations? Int J Tuberc Lung Dis. 2019;23(2):157. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6394279/. Cited 10 Feb 2023.
10. Hanifa Y, Fielding KL, Chihota VN, Adonis L, Charalambous S, Foster N et al. The utility of repeat Xpert MTB/RIF testing to diagnose tuberculosis in HIV-positive adults with initial negative result. Gates Open Research; 2022 . Available from: https://gatesopenresearch.org/articles/2-22. Cited 10 Feb 2023.
11. NICD. Weekly Influenza and Respiratory Syncytial Surveillance Report. NICD. 2013. Available from: https://www.nicd.ac.za/publications__trashed/weekly-influenza-and-respiratory-syncytial-surveillance-report/. Cited 11 Feb 2023.
12. Brennan A, Maskew M, Larson BA, Tsikhutsu I, Bii M, Vezi L et al. Prevalence of TB symptoms, diagnosis and treatment among people living with HIV (PLHIV) not on ART presenting at outpatient clinics in South Africa and Kenya: baseline results from a clinical trial. BMJ Open. 2020;10(9):e035794. Available from: https://bmjopen.bmj.com/content/10/9/e035794. Cited 21 Feb 2023.
13. Rangaka MX, Wilkinson RJ, Glynn JR, Boulle A, van Cutsem G, Goliath R et al. Effect of Antiretroviral Therapy on the Diagnostic Accuracy of Symptom Screening for Intensified Tuberculosis Case Finding in a South African HIV Clinic. Clin Infect Dis. 2012;55(12):1698–706. Available from: https://doi.org/10.1093/cid/cis775. Cited 21 Feb 2023.
14. Rie AV, Clouse K, Hanrahan C, Selibas K, Sanne I, Williams S et al. High Uptake of Systematic HIV Counseling and Testing and TB Symptom Screening at a Primary Care Clinic in South Africa. PLOS ONE. 2014;9(9):e105428. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0105428. Cited 21 Feb 2023.
15. Lawn SD, Myer L, Edwards D, Bekker LG, Wood R. Short-term and long-term risk of tuberculosis associated with CD4 cell recovery during antiretroviral therapy in South Africa. AIDS. 2009;23(13):1717. Available from: https://journals.lww.com/aidsonline/abstract/2009/08240/short_term_and_long_term_risk_of_tuberculosis.11.aspx. Cited 27 Jul 2025.
16. Gupta RK, Lucas SB, Fielding KL, Lawn SD. Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis. AIDS. 2015;29(15):1987. Available from: https://journals.lww.com/aidsonline/fulltext/2015/09240/Prevalence_of_tuberculosis_in_post_mortem_studies.12.aspx. Cited 27 Jul 2025.
17. Reid A, Scano F, Getahun H, Williams B, Dye C, Nunn P et al. Towards universal access to HIV prevention, treatment, care, and support: the role of tuberculosis/HIV collaboration. Lancet Infect Dis. 2006;6(8):483–95. Available from: https://www.thelancet.com/journals/laninf/article/PIIS1473309906705497/abstract. Cited 27 Jul 2025.
18. Shelburne SA, Visnegarwala F, Darcourt J, Graviss EA, Giordano TP, White ACJ et al. Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. AIDS. 2005;19(4):399. Available from: https://journals.lww.com/aidsonline/abstract/2005/03040/incidence_and_risk_factors_for_immune.5.aspx. Cited 27 Jul 2025.
19. Drain PK, Losina E, Parker G, Giddy J, Ross D, Katz JN et al. Risk Factors for Late-Stage HIV Disease Presentation at Initial HIV Diagnosis in Durban, South Africa. PLOS ONE. 2013;8(1):e55305. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0055305. Cited 27 Jul 2025.
20. Meintjes G, Lawn SD, Scano F, Maartens G, French MA, Worodria W et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. Lancet Infect Dis. 2008;8(8):516–23. Available from: https://www.thelancet.com/journals/laninf/article/PIIS1473309908701841/abstract. Cited 27 Jul 2025.
21. Pawlowski A, Jansson M, Sköld M, Rottenberg ME, Källenius G, Tuberculosis, Co-Infection HIV. PLOS Pathog. 2012;8(2):e1002464. Available from: https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1002464. Cited 27 Jul 2025.
22. Getahun H, Harrington M, O'Brien R, Nunn P. Diagnosis of smear-negative pulmonary tuberculosis in people with HIV infection or AIDS in resource-constrained settings: informing urgent policy changes. The Lancet. 2007;369(9578):2042–9. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(07)60284-0/abstract?is=. Cited 27 Jul 2025.
23. O'Donnell MR, Padayatchi N, Kvasnovsky C, Werner L, Master I, Robert Horsburgh C. J. Treatment Outcomes for Extensively Drug-Resistant Tuberculosis and HIV Co-infection. Emerg Infect Dis. 2013;19(3):416. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC3647656/. Cited 27 Jul 2025.
24. Bates MN, Khalakdina A, Pai M, Chang L, Lessa F, Smith KR. Risk of Tuberculosis From Exposure to Tobacco Smoke: A Systematic Review and Meta-analysis. Arch Intern Med. 2007;167(4):335–42. Available from: https://doi.org/10.1001/archinte.167.4.335. Cited 27 Jul 2025.
25. Shargie EB. Trends, challenges and opportunities in tuberculosis control in rural Ethiopia. 2006; Available from: https://www.researchgate.net/profile/Estifanos-Shargie/publication/255590195_Trends_challenges_and_opportunities_in_tuberculosis_control_in_rural_Ethiopia/links/59034b2a4585152d2e92e606/Trends-challenges-and-opportunities-in-tuberculosis-control-in-rural-Ethiopia.pdf. Cited 27 Jul 2025.
26. Horton KC, Sumner T, Houben RMGJ, Corbett EL, White RG. A Bayesian Approach to Understanding Sex Differences in Tuberculosis Disease Burden. Am J Epidemiol. 2018;187(11):2431–8. Available from: https://doi.org/10.1093/aje/kwy131. Cited 27 Jul 2025.
27. Dowdy DW, Cattamanchi A, Steingart KR, Pai M. Is Scale-Up Worth It? Challenges in Economic Analysis of Diagnostic Tests for Tuberculosis. PLOS Med. 2011;8(7):e1001063. Available from: https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001063. Cited 27 Jul 2025.
28. Getahun H, Kittikraisak W, Heilig CM, Corbett EL, Ayles H, Cain KP et al. Development of a Standardized Screening Rule for Tuberculosis in People Living with HIV in Resource-Constrained Settings: Individual Participant Data Meta-analysis of Observational Studies. PLOS Med. 2011;8(1):e1000391. Available from: https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000391. Cited 21 Feb 2023.
29. Getahun H, Kittikraisak W, Heilig CM, Corbett EL, Ayles H, Cain KP et al. Development of a Standardized Screening Rule for Tuberculosis in People Living with HIV in Resource-Constrained Settings: Individual Participant Data Meta-analysis of Observational Studies. PLOS Med. 2011;8(1):e1000391. Available from: https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000391. Cited 27 July 2025.
30. Kufa T, Mngomezulu V, Charalambous S, Hanifa Y, Fielding K, Grant AD et al. Undiagnosed Tuberculosis Among HIV Clinic Attendees: Association With Antiretroviral Therapy and Implications for Intensified Case Finding, Isoniazid Preventive Therapy, and Infection Control. JAIDS J Acquir Immune Defic Syndr. 2012;60(2):e22. Available from: https://journals.lww.com/jaids/fulltext/2012/06010/Undiagnosed_Tuberculosis_Among_HIV_Clinic.11.aspx. Cited 27 Jul 2025.
31. Yoon C, Semitala FC, Atuhumuza E, Katende J, Mwebe S, Asege L et al. Point-of-care C-reactive protein-based tuberculosis screening for people living with HIV: a diagnostic accuracy study. Lancet Infect Dis. 2017;17(12):1285–92. Available from: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(17)30488-7/abstract. Cited 27 Jul 2025.
32. Andrews JR, Lawn SD, Rusu C, Wood R, Noubary F, Bender MA et al. The cost-effectiveness of routine tuberculosis screening with Xpert MTB/RIF prior to initiation of antiretroviral therapy: a model-based analysis. AIDS. 2012;26(8):987. Available from: https://journals.lww.com/aidsonline/abstract/2012/05150/the_cost_effectiveness_of_routine_tuberculosis.10.aspx. Cited 27 Jul 2025.
33. Suthar AB, Lawn SD, del Amo J, Getahun H, Dye C, Sculier D et al. Antiretroviral Therapy for Prevention of Tuberculosis in Adults with HIV: A Systematic Review and Meta-Analysis. PLOS Med. 2012;9(7):e1001270. Available from: https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001270. Cited 12 Apr 2021.
34. Rangaka MX, Wilkinson RJ, Glynn JR, Boulle A, van Cutsem G, Goliath R et al. Effect of Antiretroviral Therapy on the Diagnostic Accuracy of Symptom Screening for Intensified Tuberculosis Case Finding in a South African HIV Clinic. Clin Infect Dis. 2012;55(12):1698–706. Available from: https://doi.org/10.1093/cid/cis775. Cited 25 Jul 2021.
35. Khan FA, Verkuijl S, Parrish A, Chikwava F, Ntumy R, El-Sadr W et al. Performance of symptom-based tuberculosis screening among people living with HIV: not as great as hoped. AIDS Lond Engl. 2014;28(10):1463–72. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5116236/. Cited 25 Jul 2021.
36. Dhana A, Hamada Y, Kengne AP, Kerkhoff AD, Rangaka MX, Kredo T, et al. Tuberculosis screening among ambulatory people living with HIV: a systematic review and individual participant data meta-analysis. Lancet Infect Dis. 2022;22(4):507–18. Available from: https://www.thelancet.com/article/S1473-3099(21)00387-X/fulltext. Cited 27 Jul 2025.
37. Cohen C, Kleynhans J, Moyes J, McMorrow ML, Treurnicht FK, Hellferscee O, et al. Asymptomatic transmission and high community burden of seasonal

influenza in an urban and a rural community in South Africa, 2017–18 (PHIRST): a population cohort study. Lancet Glob Health. 2021;9(6):e863-74. Available from: https://www.sciencedirect.com/science/article/pii/S2214109X21001418. Cited 25 Jul 2021.
38. Tedijanto C, Hermans S, Cobelens F, Wood R, Andrews JR. Drivers of seasonal variation in tuberculosis incidence: insights from a systematic review and mathematical model. Epidemiol Camb Mass. 2018;29(6):857–66. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6167146/. Cited 25 Jul 2021.
39. The South African Antiretroviral Treatment Guidelines. Final 25 March 2013 corrected. Available from: https://sahivsoc.org/Files/2013%20ART%20Treatment%20Guidelines%20Final%2025%20March%202013%20corrected.pdf. Cited 21 Feb 2023.
40. NDoD. National Consolidated Guidelines for the Management of HIV and PMTCT. 2020. TB HIV Informational Systems Support Portal. 2020. Available from: https://www.tbhivinfosys.org.za/doc/national-consolidated-guidelines-for-the-management-of-hiv-and-pmtct-2020/. Cited 21 Feb 2023.
41. HERO. 2022. Does differentiated service delivery for HIV treatment change healthcare providers workload? Provider views from Malawi, South Africa, and Zambia. Available from: https://www.heroza.org/wp-content/uploads/2022/07/Phiri-Providers-Workload_AIDS-2022-Abstract-Submission_Bevis.pdf. Cited 21 Feb 2023.
42. Huber A, Pascoe S, Nichols B, Long L, Kuchukhidze S, Phiri B, et al. Differentiated Service Delivery Models for HIV Treatment in Malawi, South Africa, and Zambia: A Landscape Analysis. Glob Health Sci Pract. 2021;9(2):296–307. Available from: https://www.ghspjournal.org/content/9/2/296. Cited 21 Feb 2023.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.