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Focused ultrasound to diagnose HIV-associated tuberculosis (FASH) in the extremely resource-limited setting of South Sudan: a cross-sectional study

Flavio Bobbio,[1] Francesco Di Gennaro,[2] Claudia Marotta,[3] John Kok,[4] Gabriel Akec,[4] Luca Norbis,[5] Laura Monno,[2] Annalisa Saracino,[2] Walter Mazzucco,[6] Marta Lunardi[7]

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For numbered affiliations see end of article.

Correspondence to
Dr Flavio Bobbio;
flavio.bobbio@gmail.com

ABSTRACT

Objective Our cross-sectional study aimed at evaluating the diagnostic performance of Focused Assessment with Sonography for HIV-associated tuberculosis (FASH) to detect extrapulmonary tuberculosis in extremely resource-limited settings, with visceral leishmaniasis as a differential diagnosis with overlapping sonographic feature.

Design Cross-sectional study.

Setting Voluntary Counselling and Testing Centre (VCT) of Yirol Hospital, South Sudan.

Participants From May to November 2017, 252 HIV-positive patients out of 624 newly admitted to VCT Centre were registered for antiretroviral treatment. According to the number of trained doctors available to practise ultrasound (US) scan, a sample of 100 patients were screened using the FASH protocol.

Interventions Following a full clinical examination, each patient was scanned with a portable US scanner in six different positions for pleural, pericardial, ascitic effusion, abdominal lymphadenopathy and hepatic/splenic microabscesses, according to the FASH protocol. A k39 antigen test for visceral leishmaniasis was also performed on patients with lymphadenopathy and/or splenomegaly. All demographic, clinical and HIV data, as well as FASH results and therapy adjustments, were recorded following the examination.

Results The FASH protocol allowed the detection of pathological US findings suggestive of tuberculosis in 27 out of the 100 patients tested. Overall, FASH results supported tuberculosis treatment indication for 16 of 21 patients, with the treatment being based exclusively on FASH findings in half of them (8 patients). The group of FASH-positive patients had a significantly higher proportion of patients with CD4 count below 0.2 x10^9/L (n=22, 81%) as compared with FASH-negative patients (n=35, 48%) (p=0.003). Moreover, 48% (n=13) of FASH-positive patients had CD4 below 100 cells/mm^3. All patients tested had a negative result on k39 antigen test.

Conclusion FASH was found to be a relevant diagnostic tool to detect signs of tuberculosis. Further research is needed to better define a patient profile suitable for investigation and also considering diagnostic accuracy.

Strengths and limitations of this study

- Our study analysed the yield of the diagnostic ultrasound FASH (Focused Assessment with Sonography for HIV-associated tuberculosis) protocol in detecting extrapulmonary tuberculosis in HIV-positive patients from an extremely resource-limited setting of rural African, without any other diagnostic opportunities.
- It is worth mentioning that South Sudan is one of the poorest countries in Africa, with a huge need to address health and to meet healthcare demand.
- All ultrasound examinations were performed by a single clinician trained in using ultrasound.
- This is a single-centre experience with a relatively small number of patients recruited.
- Unavailability of a definitive microbiological diagnosis and lack of follow-up were the main limitations of the study.

BACKGROUND

In sub-Saharan Africa, the concomitant high burden of both HIV and tuberculosis (TB) has led to an increasing incidence of extrapulmonary tuberculosis (EPTB).[1]

EPTB is found more frequently in HIV-positive than in HIV-negative individuals, and the diagnosis is often challenging even in high-income countries due to the low sensitivity and specificity of many available diagnostic tests and broad differential diagnoses.[2 3]

Ultrasound (US) can aid in the diagnosis of a variety of infectious diseases including EPTB, and the point-of-care ultrasound (POCUS) application is useful especially in resource-limited settings.[4–6]

Focused Assessment with Sonography for HIV-associated tuberculosis (FASH) is a US protocol aimed to detect sonographic signs of EPTB in patients with HIV infection.[7] The examination is focused to find effusions (pericardial, pleural, peritoneal), intra-abdominal lymph nodes enlargement and microabscesses, especially in the spleen and

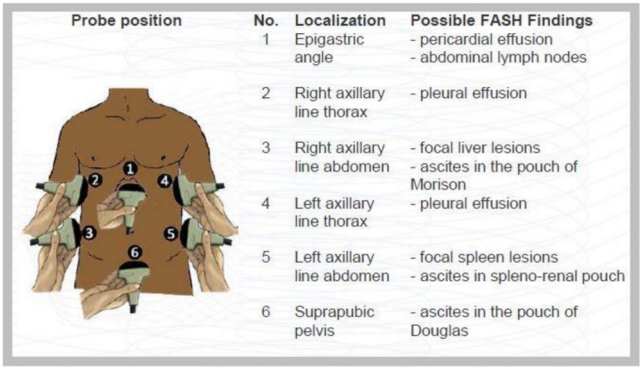

Figure 1 FASH examination protocol: probe positions and findings (from Focus Assessment with Sonography for HIV/TB. A practical Manual, Tom Heller, 2013, TALC, with permission from the author). FASH, Focused Assessment with Sonography in HIV-associated tuberculosis.

also in the liver, using six standard scanning planes in the abdomen and lower thorax (figure 1).[7]

POCUS plays a fundamental role in the diagnosis of different infectious conditions in contexts with limited resources, for example, TB, echinococcosis, amoebic liver abscess, intestinal schistosomiasis and visceral leishmaniasis.[4] In particular, within the context of POCUS, FASH protocol was demonstrated to be very useful in the diagnosis of TB in both HIV-positive and HIV-negative subjects, including children and adults.[8–10]

Currently, in low-income countries with limited infrastructure and weak health systems, especially in terms of qualified human resources, treatment for EPTB is often started based exclusively on a clinical case definition.[11 12] This is especially true for South Sudan, the youngest country in the world which has been suffering from years of civil war, economic downturn and famine. Endemic seasonal diseases such as malaria and a recent cholera outbreak (June 2016–February 2018)[13] affect South Sudan's people and further strain the already weak health system.

Our study aimed to (1) evaluate the diagnostic role of FASH for EPTB in an extremely low-resource setting as Yirol Hospital, South Sudan; and (2) provide information on visceral leishmaniasis as potential relevant differential diagnosis with similar sonographic features so requiring a different management in the same context.

METHODS

Study setting and design

An observational, cross-sectional study was designed and implemented at the Voluntary Counselling and Testing Centre (VCT) of Yirol Hospital in Eastern Lakes State, South Sudan. Yirol Hospital serves as a referral institution for the entire Eastern Lakes State, which has an estimated 442 000 inhabitants.[14] Yirol Hospital has no X-ray services available and no health facilities capable of X-ray exams within reasonable distance. The VCT Centre tests patients for HIV infection in accordance with the regulations and guidelines of the Ministry of Health of South Sudan and is authorised to provide antiretroviral treatment (ART) both for inpatients and outpatients. Subjects referred to VCT for counselling and testing are quite diversified and can be categorised into the following: (1) admitted to hospital wards (mainly medical) and sent to the centre for clinical reasons by doctors or clinical officers; (2) sent to VCT by clinical officers of the outpatient department of the hospital; (3) spontaneously coming to the centre for testing; and (4) under TB treatment and also tested positive for HIV (in South Sudan, the treatment of TB is managed by a specific non-governmental organisation that is not integrated in the hospital), or relatives to patients already enrolled.

From May to November 2017, 624 new adult patients accessed the VCT Centre of Yirol Hospital. Among these patients, 252 (40%) were positive for HIV according to the clinical guidelines used in South Sudan (Determine + Unigold).[13] These patients were prospectively approached for consecutive enrolment in the study according with the availability of doctors trained for the US scan.

Following informed consent, each patient enrolled underwent a careful history and physical examination (vital signs, weight, height, and diastolic and systolic blood pressure, along with chest, abdomen and lymph node examination). Clinical staging according to the WHO classification (clinical guidelines of South Sudan for HIV) was done before US scan using clinical data only, following the protocol for all patients registered at VCT. Clinical symptoms suggestive of TB (cough, weight loss, haemoptysis, night sweats, fatigue) were enquired, and information on previous TB treatment, isoniazid preventive therapy and ART history was recorded. Acid-fast bacilli sputum smears were carried out when necessary and feasible (presence of chronic cough with sputum), while CD4 counts were done for all patients (PIMA Analyser, Alere, Jena, Germany). For patients with lymphadenopathy (presence of lymph nodes with at least a long axis diameter of more than 1.5 cm) and/or splenomegaly (bipolar axis >13 cm), k39 antigen test, a rapid test for visceral leishmaniasis, was performed (Kala-Azar test, Oscar Medicare, New Delhi, India).

At completion of the clinical examination, sonographic scans were performed according to the FASH protocol.[7] In brief, each patient was scanned in six different positions (figure 1) using a portable black-and-white US scanner with convex (3.5 MHz) probe and linear (7 MHz) probe (May–October: DP-30, Mindray; November: M7 Premium, Mindray, Nanshan Shenzhen, People's Republic of China). All US examinations were performed by a single clinician trained in US. At the end of each examination, the clinician subjectively rated the quality of the US views as 'excellent', 'satisfactory' or 'problematic'. All demographic, clinical and HIV data, as well as FASH results and therapy adjustments, were recorded following the examination.

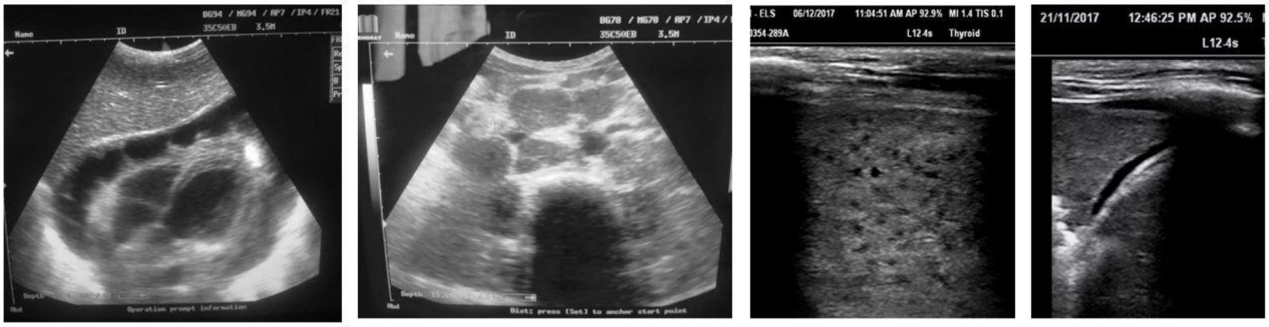

Figure 2 Examples of ultrasound findings in patients with positive results on FASH examination admitted to Yirol Hospital, South Sudan. (A) Pericardial effusion, (B) periportal/para-aortic lymph nodes (>1.5 cm in diameter), (C) focal splenic lesions, and (D) pleural effusion and consolidation of the lungs. FASH, Focused Assessment with Sonography in HIV-associated tuberculosis.

According to FASH protocol, the examination was considered positive (FASH+) if at least one of the following US abnormalities was detected:

- Pericardial effusion (figure 2A).
- Periportal/para-aortic lymph nodes (>1.5 cm in diameter) (figure 2B).
- Focal splenic lesions (figure 2C).
- Pleural effusion or consolidation of the lung (figure 2D).
- Ascites without alternative explanation.
- Focal liver lesions.

It is important to note that TB treatments in South Sudan are delivered by a network of centres that are not directly related to government hospitals nor with the centres providing ART. It was thus of paramount importance to develop close relationship and trust between TB and ART centres. The TB centre in Yirol was informed about the study and agreed to initiate TB treatment based on US and clinical results.

Statistical analysis

Categorical variables were reported as absolute and relative frequencies (percentages). X^2 test (with Fisher's correction as required) was used to compare categorical variables using STATA V.13. All statistical tests were two-tailed and statistical significance was assumed for a p value <0.05.

Patient and public involvement

The research question was born to respond to the health needs of the poorest country in the world. The idea was to apply a transportable, economic method, easily applicable to the HIV and TB service in South Sudan. Patients and doctors at the Yirol Hospital were involved to better understand how to improve the project by sharing their own idea. The results of this study will be disseminated through a final report and other activities within the hospital and surrounding communities.

RESULTS

Overall, 100 patients (52% female) were enrolled in the study and underwent full clinical examination followed by a FASH US evaluation. Table 1 summarises the demographic and clinical characteristics of the whole patient cohort stratified by FASH results (positive vs negative). Abnormal US findings consistent with FASH positive exams were detected in 27 (27%) patients.

The FASH-positive patients group had a significantly higher proportion of patients with CD4 count below 0.2 $x10^9/L^3$ (n=22, 81%) as compared with FASH-negative patients (n=35, 48%) (p=0.003); moreover 48% (n=13) of FASH-positive patients had CD4 below 100 cells/mm^3.

WHO HIV stage significantly differed in the two groups (p=0.001), with a higher proportion of stage III (n=17, 63%) and stage IV (n=5; 18%) in FASH-positive patients as compared with the negative ones. Of the FASH-positive patients, 93% (n=25) were ART-naïve, even if no statistical difference was documented with the comparison group (p=0.177). The proportion of patients accessing a previous TB treatment was significantly higher (p=0.003) in FASH-positives (n=7, 26%) as compared with patients who are FASH-negative (n=3, 4%). A borderline statistical difference was highlighted between positive and negative FASH patients with regard to pharmacological TB prophylaxis (p=0.059), this practice being more frequently reported in FASH-positive patients (n=10, 37%) than in negative ones (n=13, 18%).

FASH positivity results, according to WHO HIV stage, are shown in figure 3. The proportion of FASH positivity significantly increases with the stage as compared with FASH-negative group (p=0.001).

In table 2 are reported additional diagnostic results of the 27 patients with US pathological findings. Sputum test was positive in 5 of the 27 patients (18%), while all the patients tested for k39 had negative results. Eighty-eight per cent of FASH-positive patients were symptomatic, but clinical examination resulted negative in 74% (n=20) of patients for palpable lymph adenopathies, in 89% (n=24)

Table 1 Demographic and clinical characteristics of 100 patients recruited at Yirol Hospital, South Sudan, stratified by FASH results

	Total (N=100)	FASH-positive (n=27)	FASH-negative (n=73)	P value
Demographic characteristics				
Gender				
Male	48 (48)	12 (44)	36 (49)	0.82
Female	52 (52)	15 (55)	37 (51)	
Age				
18–30	34 (34)	6 (22)	28 (38)	0.26
31–40	44 (44)	12 (44)	32 (44)	
41–50	14 (14)	6 (22)	8 (11)	
>50	8 (8)	3 (11)	5 (7)	
Address				
Yirol Town	36 (36)	14 (52)	22 (30)	0.272
Yirol East	35 (35)	8 (30)	27 (37)	
Yirol West	22 (22)	4 (15)	18 (25)	
Other	7 (7)	1 (4)	6 (8)	
Setting				
Inpatient	58 (58)	19 (70)	39 (53)	0.17
Outpatient	42 (42)	8 (30)	34 (47)	
Clinical characteristics				
Body mass index (kg/m^2)				
Low <18	83 (89)	20 (74)	63 (86)	1
Normal 18–25	9 (10)	2 (7)	7 (10)	
High >25	1 (1)	0 (0)	1 (1)	
CD4				
0.2 x10^9/L	57 (57)	22 (81)	35 (48)	0.003
WHO HIV stage				
I	13 (13)	0 (0)	13 (18)	0.001
II	30 (30)	5 (18)	24 (33)	
III	50 (50)	17 (63)	33 (45)	
IV	7 (7)	5 (18)	2 (3)	
Previous antiretroviral treatment				
Yes	3 (3)	2 (7)	1 (1)	0.177
No	97 (97)	25 (93)	72 (99)	
Previous TB treatment				
Yes	10 (10)	7 (26)	3 (4)	0.003
No	90 (90)	20 (74)	70 (96)	
TB prophylaxis				
Yes	23 (23)	10 (37)	13 (18)	0.059
No	77 (77)	17 (63)	60 (82)	

FASH, Focused Assessment with Sonography in HIV-associated tuberculosis; TB, tuberculosis.

for lung abnormalities and in 85% (n=23) for abdomen abnormalities.

The pathological findings documented in the 27 FASH-positive patients are summarised in table 3. Of the three patients with ascites, one had an additional pleural effusion and one had splenic microabscesses. With regard to one patient with ascites as the only finding, as no other cause for ascites was detected (normal liver, spleen,

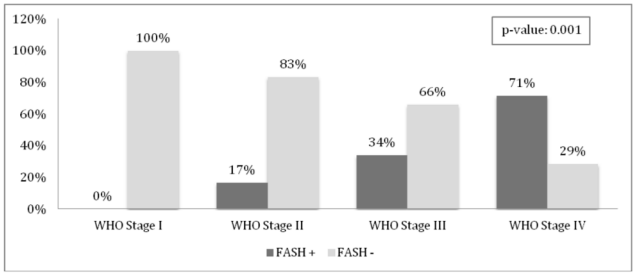

Figure 3 WHO HIV stage according to FASH positivity among the 100 enrolled patients at Yirol Hospital, South Sudan. FASH, Focused Assessment with Sonography in HIV-associated tuberculosis.

heart and kidneys) and his CD4 count was very low (28 cells/mm^3), also in light of the presence of a clinical wasting syndrome, it was decided to start TB treatment.

TB treatment was initiated in 21 (21%) patients after complete clinical and diagnostic examination (table 4). Overall, FASH results supported TB treatment indication in 76% (n=16) of all patients started; of interest, in half of them (n=8), treatment was based exclusively on FASH findings.

Table 2 Additional diagnostic characteristics of the 27 patients with positive results on FASH examination, admitted to Yirol Hospital, South Sudan

Sputum test	
Positive	5 (18)
Negative	13 (48)
Not done	12 (44)
Kala-Azar test	
Negative	13 (48)
Not done	14 (52)
Symptoms	
Yes	24 (89)
No	3 (11)
CD4 (cells/mm^3)	
<100	13 (48)
>100 to ≤200	9 (33)
>200	5 (18)
Lymph nodes clinical examination	
Yes	7 (26)
No	20 (74)
Lung clinical examination	
Positive	3 (11)
Negative	24 (89)
Abdomen clinical examination	
Positive	4 (15)
Negative	23 (85)

FASH, Focused Assessment with Sonography in HIV-associated tuberculosis.

Table 3 Sonographic findings in 27 patients with positive FASH examination, admitted to Yirol Hospital, South Sudan

Pathological findings	n (%)
Periportal/para-aortic lymph nodes	15 (55)
Pericardial effusion	9 (33)
Lung consolidation	8 (30)
Pleural effusion	5 (18)
Splenic focal lesions	4 (15)
Ascites	3 (11)
Ascites in the pouch of Douglas	3 (11)
Liver focal lesions	1 (4)
Ascites in the splenorenal pouch	1 (4)
Ascites in the hepatorenal pouch (Morison's pouch)	0 (0)

FASH, Focused Assessment with Sonography in HIV-associated tuberculosis.

Out of 27 patients with abnormal FASH results, only 18 started TB treatment. Several reasons determined this clinical decision: two patients with pericardial effusion left the hospital before starting treatment; five were positive for pleural effusion or lung consolidation and were first treated as pneumonia with improvement; one showed a single focal hypoechoic lesions of the liver with an axis of 2 cm and was addressed to start ART treatment with a strict follow-up of the liver lesion; and one patient with abdominal lymph nodes, peritoneal and pleural-free effusion and splenic hypoechoic lesions died before initiating TB treatment. All patients (n=13) with enlarged lymph nodes, splenomegaly or splenic lesions were tested for antibody against k39 protein and all tests were negative.

The quality of the US examination rated by the clinician was 'excellent' in 39% (n=39) and 'satisfactory' in 56% (n=56); 5% (n=5) of the exams were considered 'problematic'.

Table 4 Indications for TB treatment initiation in 21 patients among the 100 enrolled at Yirol Hospital, South Sudan

Indication for TB treatment initiation	n (%)
Only FASH	8 (38.1)
Only sputum test	0 (0)
Only clinical reasons	2 (14.3)
FASH + sputum test	4 (19.0)
FASH + clinical reasons	3 (14.3)
Sputum test + clinical reasons	2 (9.5)
FASH + sputum + clinical reasons	1 (4.8)
Total FASH	16 (76.2)
Total sputum test	8 (38.1)
Total clinical reasons	5 (23.8)

FASH, Focused Assessment with Sonography in HIV-associated tuberculosis; TB, tuberculosis.

DISCUSSION

This observational study evaluated the yield of a diagnostic tool (FASH) for EPTB in Eastern Lakes State (Yirol Hospital), South Sudan. The FASH protocol allowed the detection of pathological US findings suggestive of TB in 27 out of the 100 patients tested.

The most frequent pathological findings documented were periportal/para-aortic lymph nodes, pericardial effusion and lung consolidation. FASH findings were more likely to be detected in patients with advanced HIV disease with CD4 count <200 cells/mm^3, WHO stage III/IV and low body mass index (BMI). The quality of the US view was mostly rated as excellent and satisfactory by the clinician performing the examination.

Our findings support the important role of this simple, inexpensive and fast technique in resource-limited setting as the Yirol Hospital.[15–17] Moreover, we were able to identify a core group with the highest yield in FASH, represented by patients with low BMI, low CD4 and advanced WHO stage.

FASH can be taught rapidly to physicians with limited or no prior US experience.[18] In high prevalence setting, the learning process is facilitated by the presence of pathological findings in a large proportion of HIV/TB coinfected patients,[19–22] which is supported by our data. Moreover, the fact that many patients under investigation are underweight makes scanning easier, as abdominal volume interfering with scanning becomes less relevant. The examination takes only a few minutes and may provide important findings with a direct and significant impact on patient management.[2 23] Nevertheless, an important operational question is related to operators who can reliably use this diagnostic technique. In our single-centre experience, we did not succeed in motivating the local clinical officers of the hospital to be trained in the use of US. Young clinicians seemed absolutely more motivated. This is probably related to the poor capacity of the lower cadre of clinical staff in using diagnostic imaging tools and to the fact that the clinical officers in Yirol Hospital are not exclusively dedicated to the care of patients with HIV, and they had many concurrent competing tasks and activities.

Although the diagnosis of EPTB based on abnormal US examination is not certain, it is justified to start a TB treatment based on these findings considering data from the literature and the lack of any other diagnostic tools for further work-up in a rural health setting.

In the region where the study was conducted, there are no epidemiological data for *Leishmania* spp infection, but this infectious disease is known to be locally prevalent in South Sudan. According to the documents of the Ministry of Health of South Sudan, visceral leishmaniasis is endemic in four states in South Sudan, namely Upper Nile, Unity, Jonglei and Eastern Equatoria; 2.7 million people are considered to be at risk in 28 counties.[24–26] For this reason, we also tested patients for visceral leishmaniasis as this could be considered a potential differential diagnosis with overlapping imaging findings of enlarged lymph nodes and spleen lesions. With the sensitivity and specificity of the immunochromatographic strip test being more than 90%,[27] by using the k39 antigen test in patients with an abnormal US result we were able to exclude the presence of visceral leishmaniasis.

Our study has some limitations, which include the relatively small number of patients, the unavailability of a definitive microbiological diagnosis and the lack of follow-up, but we believe our results remain relevant in light of the study setting. South Sudan is a country devastated by civil war, economic downturn and health epidemics such as cholera. As reported by previous studies conducted in such a deprived context with a vulnerable target population affected by HIV-related diseases,[28 29] healthcare organisational models, human and technical resources, especially the availability of diagnostic tests, may have relevant implications on the pathways of care dedicated to patients with HIV.[30]

There is an increasing interest in employing US in low-income and middle-income countries given its relatively steep learning curve, ionisation radiation-free nature and its increasing availability at reasonable costs.[4 17 31] Moreover, it can be portable and can operate with batteries, being independent from a stable electric power supply.[4] US gel, the only routine supply item needed, can be easily produced locally, thus making US an attractive option in resource-limited settings.[16] On the other hand, some concern remains about the intrinsic interobserver variability and the potential for diagnostic errors, which should moreover be investigated specifically for TB. While the conditions for a wider implementation are favourable, few studies have been performed in low-income countries especially in rural settings. Our observation adds to the available evidence indicating that the use of FASH for the diagnosis of TB can be useful in this setting.

CONCLUSIONS

FASH was found to be a relevant diagnostic tool to detect signs of EPTB, even in an extremely resource-limited setting such us South Sudan, where HIV and TB incidence is high and radiological and microbiological investigations are scarce. Our data contributed data to better characterise a patient population with the highest yield, namely patients with low BMI, low CD4 and advanced WHO stage, while further research that considers feasibility and diagnostic accuracy is needed. Other interesting fields requiring further research include the training of health operators and the shifting of the procedure to the local staff.[30]

Author affiliations
[1]Doctors With Africa CUAMM, Yirol, South Sudan
[2]Infectious Diseases, University of Bari, Bari, Italy
[3]Department of Sciences for Health Promotion and Mother to Child Care G.D Alessandro, University of Palermo, Palermo, Italy
[4]Yirol Hospital, Yirol, South Sudan
[5]Ospedale San Raffaele, Milano, Lombardia, Italy

[6]Department of Sciences for Health Promotion and Mother to Child Care G.D Alessandro, University of Palermo, Palermo, Italy
[7]Doctors With Africa CUAMM, Yirol, South Sudan

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study protocol was submitted to the State Ministry of Health in Juba and to the Local Ministry of Health in Yirol and was approved by the ethical committee of the State Ministry of Health of South Sudan in April 2017 (Authorisation MOH/ERB33/2018). Informed consent was obtained from all participants together with consent for HIV testing.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The data that support the findings of this study are available on demand from the authors upon reasonable request and with permission from Doctors with Africa Cuamm.

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