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Standard of care in advanced HIV disease: review of HIV treatment guidelines in sub-Saharan African countries—an extension study of eight countries

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Abstract

Introduction The World Health Organization (WHO) has published guidelines for the management of patients with advanced HIV disease (AHD) but mortality remains high. Adoption of WHO recommendations by national guidelines is poorly documented. We aimed to extend our prior review of six national management guidelines by including additional countries from sub-Saharan Africa.

Methods We identified guidelines of eight additional countries participating in a multicountry trial of azithromycin prophylaxis for AHD. Data was extracted in five domains including definition of AHD (1 item), screening (6 items), prophylaxis (6 items), supportive care (1 items), and HIV treatment (4 items) and scored agreement of each national guideline with the WHO guidelines.

Results Six of the eight national guidelines had a designated section for AHD. Compared with the WHO guideline, the agreement score for national guidelines was between 7 and 17 out of 18, whereby disagreement is mainly driven by missing information. None of the national guidelines had more than three items not in agreement with the WHO guidelines, and the maximum number of items not addressed by any one guideline was eight. Main areas of disagreement were the targeted population for start of ART in presence of tuberculosis meningitis (1/8 in agreement) and urine lipoarabinomannan screening (2/8 in agreement). The targeted population group for cotrimoxazole prophylaxis and its discontinuation was in line with the WHO recommendations in 3/8 national guidelines. Except one guideline, all documents showed similar overall agreement, irrespectively of publication date.

Conclusion National guidelines for the management of people with AHD are broadly in agreement with WHO guidelines. Main areas of disagreement are recommendations regarding urine lipoarabinomannan screening, cotrimoxazole prophylaxis and start of antiretroviral therapy in presence of tuberculosis.

Keywords Advanced HIV disease, Guidelines, Sub-Saharan Africa, Antiretroviral therapy

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Introduction

Advanced HIV disease (AHD), defined as a CD4 count of < 200 CD4 + cells/mm^3 or World Health Organization (WHO) clinical stage 3 or 4, affects about 4 million adults globally [1–3]. People with AHD are at high risk of death in the first months after entering or re-entering care, with progressively higher mortality in those with lower CD4 counts [4–6]. Even in the setting of a contemporary randomized controlled trial investigating enhanced prophylactic treatments, more than 10% of participants died within six months [7]. The cause of death is often unknown, but opportunistic and bacterial infections are likely key drivers [8].

Guidelines for the management of people with AHD were first published by the WHO in 2017 [2]. These guidelines provide evidence-based recommendations, including diagnosis, prophylaxis and pre-emptive treatment, and adherence support. Subsequent updates have incorporated emerging evidence and highlighted specific aspects such as care of people with AHD who are seriously ill and the diagnosis of opportunistic infections [9, 10].

We have previously reported on the uptake of the WHO guideline recommendations in national guidelines of six countries in sub-Saharan Africa who participated in the vanguard phase of the *Reducing Mortality In Adults With Advanced HIV Disease* trial (REVIVE trial, NCT05580666) [11]. Since our previous publication, the REVIVE trial has expanded to include an additional eight countries. Here, we evaluate the uptake by national guidelines from these eight countries of the latest WHO guideline AHD recommendations as summarized in the 2021 document "*Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach*" [12].

Methods

The methodology for this review was identical to the previously published report and described in detail there [11]. In brief, lead investigators of participating countries provided national guideline documents outlining the management of people with AHD. Data for the following categories were extracted from national guidelines and the WHO 2021 document:

1. Definition of AHD (1 item)
2. Screening (6 items)
3. Prophylaxis (6 items)
4. Supportive care (1 item)
5. HIV treatment (4 items)

Extracted data was presented to the national investigator to review and validate. Disagreements regarding the accuracy of the extracted data were resolved by discussion.

National guideline recommendations were compared with those in the WHO 2021 document and scored as follows: Not addressed (0 points): no information for the respective item was found within the national guidelines. No agreement (also 0 points): national recommendation not in line with the WHO 2021 guidelines. Agreement (1 point): extracted data for an item in the national guideline matched the WHO 2021 guideline recommendations. Partial agreement (0.5 points): data of the national guideline included similar but not identical criteria (e.g., WHO 2021: CD4 + < 100 cells/mm^3, National guideline: CD4 + < 200 cells/mm^3). Scores were calculated for each national guideline and presented as bar graphs. Overall agreement was presented based on the publication year of the guideline.

Results

We reviewed national guidelines from the following eight countries: Ethiopia, Ghana, Ivory Coast, Mozambique, Republic of Congo, Rwanda, Tanzania, and Zambia [13–20]. Six had a specific section for AHD. Guidelines were published between 2019 and 2023.

Information extracted from national guidelines is presented in Table 1 and agreement with the WHO 2021 document in Table 2. The index of assessed guidelines is shown in Table 3.

Definition of AHD

The Ivory Coast guideline did not include a definition of AHD. All other national guidelines employed the same definition as the WHO, considering a CD4 + cell count < 200 cells/mm^3 or a WHO clinical stage 3 or 4 disease as AHD.

Screening

CD4 testing

All national guidelines recommended CD4 count testing for people with HIV (PWH) entering or re-entering antiretroviral therapy (ART) care, which is in line with the WHO 2021 recommendations. However, the Republic of Congo recommended performing CD4 testing only for those in whom ART is started.

Cryptococcal disease

Except of Ivory Coast, all guidelines recommended serum cryptococcal antigen testing, but there were differences in the population to be tested, resulting in partial agreement for the documents of Mozambique, Tanzania, and Zambia. Based on the WHO guideline

Table 1 Extracted data country specific guidelines

	WHO 2021	Ethiopia	Ghana	Ivory Coast	Mozambique	Republic of Congo	Rwanda	Tanzania	Zambia
Guideline information									
Country specific guideline	N/A	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Year of publication	2021	2022	2022	2019	2023	2023	2022	2019	2022
Specific section for AHD	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Definition of AHD									
Definition	<200 CD 4+ cells/mm3 or WHO clinical stage 3 or 4	CD4 cell count <200 cells/mm^3 or WHO stage 3 or 4 event	CD4 cell count of less than 200 cells/mm^3 or WHO clinical stage 3 or 4 disease	Not addressed	CD4 <200 cells/mm^3 or WHO clinical stage 3 or 4 disease	CD4 <200 cells/mm^3 or WHO clinical stage 3 or 4 disease	CD4 cell count <200 cells/mm^3 or a WHO clinical stage 3 or 4 event	CD4 count <200 cells/mm^3 or WHO clinical stage 3 or 4	CD4 cell count <200 cells/mm^3 or WHO stage 3 or 4 event
Screening									
CD4 testing at baseline	Yes	Yes	Yes	Yes	Yes	Yes, if starting ART	Yes	Yes	Yes
Cryptococcal antigen	Yes	Yes	Yes	Not addressed	Yes	Yes	Yes	Yes	Yes
- **Population group**	- Recommended: <100 CD 4+ cells/mm3 - Considered: <200 CD 4+ cells/mm3	<100 CD 4+ cells/mm^3	Recommended for <100 cells/mm^3 and considered for 200cells/mm^3	Not addressed	- CD4<200 cells/mm^3 or WHO stage 3 or 4 - Danger signs	<100 CD 4+ cells/mm^3	≤ 100 cells/mm^3, can consider if <200 cells/mm^3	CD4 <200 cell/mm^3	≤200 cells/mm^3
					- Suspect of Cryptococcal disease				
Routine TB screening	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
- **Urine LAM**	Yes	Yes	Yes	Not addressed	Yes	Yes	Yes	Yes	Yes
○ **Population group**	- Inpatients ≤200 CD 4+ cells/mm3 - Outpatients ≤100 CD 4+ cells/mm3 - Any CD 4+ count with symptoms or if seriously ill[h]	- ≤200 cells/mm^3 (inpatient) ≤100 cells/mm^3 (outpatient) Or any CD4 count with TB symptoms or if seriously ill	≤200 cells/mm^3 (inpatient) ≤100 cells/mm^3 (outpatient) Or any CD4 count with symptoms or if seriously ill	Not addressed	CD4 <200 cells/mm^3 or danger signs	CD4 <200 cells/mm^3 or severely ill	≤200 cells/mm^{3}or at any CD4 cell count value if seriously ill, can consider for CD4 <200 cells/mm^3	- CD4 count of less than 200 cells/uL or - who present with one of the four danger signs[c]	- ≤200 cells/mm^3 - at any CD4 count if seriously ill - Symptoms or signs of TB
Prophylaxis									
Cotrimoxazole	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
- **Population group**	- <350 CD 4+ cells/mm3 or WHO clinical stage 3 or 4 - any CD4 count in settings with high prevalence of malaria or severe bacterial infection	- <350 CD 4 cells/mm3 or WHO clinical stage 3 or 4 - All HIV/TB co-infections	- Adults with CD4 count ≤350 cells/mm^3 or WHO clinical stage 3 or 4. - Any CD4 count in settings with high prevalence of malaria or severe bacterial	Everyone tested positive for HIV independent of CD4	≤350 cells/mm3 or WHO clinical stage 2, 3 or 4.	All, regardless of clinical stage and CD4 value	- ≤350 cells/mm3 or WHO clinical stage 3 or 4 events. Any CD4 cell count value in settings with a high prevalence of malaria and/or severe bacterial infections or per	- CD4 cell count ≤350 cells/mm3 - All HIV-infected persons with active TB	≤350 cells/mm^3 or clinical stage 3 or 4

Table 1 (continued)

			infections. - HIV-infected people with active TB disease regardless of CD4+ cell counts				national guidelines - All existing patients of 5 years old and above not suppressing their viral load (VL>200 RNA copies/ml) - Cotrimoxazole shall be reintroduced in patients failing ART if the CD4 count falls below 200 cells/mm^3. - Routine co-trimoxazole prophylaxis should be given to all people living with HIV with active TB, regardless of CD4 cell count		
- **discontinuation**	- Clinically stable on ART[d], with evidence of immune recovery and/or viral suppression[e,f] - Malaria and /or severe bacterial infections are highly prevalent: co-trimoxazole prophylaxis should be continued regardless of CD4 cell count or WHO clinical stage	Clinically stable[a] with: - Evidence of immune recovery and/or viral suppression (CD4 >350 cells/mm^3 with viral load suppression) - Two consecutive CD4 count >350 cells/mm^3 if no VL result	Adults with HIV infection who are established on ART *, with evidence of immune recovery and viral suppression. [b]	Patients on ART, regular follow up for at least 3 years with good compliance and CD4>500 cell/mm^3	- CD4 ≥ 350 cells/mm^3 after 1 year on ART	For life	Not addressed	- ART is initiated and CD4 cell count is above 350 cells/ml in adults and adolescents and virological suppression	- 2 consecutive CD4 counts that are > 350 cells/mm^3
Pre-emptive therapy for cryptococcal antigenemia	Yes	Yes	Yes	Not addressed	Yes	Yes	Yes	Yes	Yes
TB preventive therapy	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
- **Population group**	Any	Any	Any	Any	Any	Any	Any	Any	Any
Supportive care									
Specified adherence information	Yes	Yes	Yes	Not addressed	Yes	Yes	Yes	Not addressed	Yes
HIV treatment									
Recommended 1st line ART	DTG/3TC/TDF OR DTG/FTC/TDF	TDF/3TC/DTG	TDF/3TC (or FTC)/DTG	TDF/3TC /DTG	TDF/3TC/DTG	TDF/3TC /DTG	TDF/3TC/DTG	TDF/3TC/DTG	TDF/XTC/DTG
Delayed/Deferred ART start after start of TB/cryptococcal treatment									
- **TB at non-neurological site**	within 2 weeks	Within 2 weeks	ART must be started as soon as practicable within two weeks but not later than 8 weeks	2 weeks	Within 2 weeks	Within 2 weeks	- CD4 cell count <=50: Start ART within 2 weeks - CD4 cell count >50: Start ART between 4-6 weeks	Within 2 weeks	Within 10 days

Table 1 (continued)

			of starting TB treatment						
- **TB meningitis**	4 – 8 weeks	4 - 8 weeks	ART must be started as soon as practicable within two weeks but not later than 8 weeks of starting TB treatment	One month	8 weeks	Not addressed	4-6 weeks	Within 2 weeks	4-6 weeks
- **Cryptococcal meningitis**	4 – 6 weeks	4 - 6 weeks	4 – 6 weeks	Not addressed	4-6 weeks	Not addressed	4-6 weeks	5 weeks	Not addressed

green: reference (WHO 2021)

[a] Individuals on ART for at least one year without any new WHO clinical stage 2, 3 or 4 events

[b] The corresponding footnote in the guideline cannot be identified

[c] Respiratory rate greater than 30 breaths/minute, temperature exceeding 39 °C, heart rate more than 120 beats/minute, and/or unable to walk unaided

[d] Clinically stable adults are defined as individuals receiving ART for at least one year without any new WHO clinical stage 2, 3, or 4 events

[e] CD4 cell count > 350 cells/mm^3, with suppression of viral loads, is considered immune recovery (some countries may adopt a threshold of CD4 cell count > 500 cells/mm^3)

[f] WHO recognizes that in settings with low prevalence of malaria and severe bacterial infection in which co-trimoxazole is used primarily as prophylaxis for some AIDS-associated opportunistic infections (Pneumocystis jirovecii pneumonia and toxoplasmosis), guidelines exist for adults living with HIV discontinuing co-trimoxazole when there is evidence of suppressed viral loads and immune recovery at CD4 cell count > 200 cells/mm^3 and they have been receiving ART for at least one year

[g] "Seriously ill" is defined based on four danger signs: respiratory rate of more than 30/min, temperature of more than 39 °C heart rate of more than 120/minute and unable to walk unaided

[h] Respiratory rate ≥ 30 breaths per minute; heart rate ≥ 120 beats per minute; or unable to walk unaided

3TC Lamivudine

AHD advanced HIV Disease

ART anti retroviral therapy

DTG Dolutegravir

FTC Emtricitabine

LAM lipoarabinomannan

TDF Tenofovir dixoproxil fumerate

(recommended < 100 cells/mm^3, considered: < 200 CD4 + cells/mm^3) we counted < 100 cells/mm^3 as agreement and < 200 CD4 + cells/mm^3 as partial agreement. Tanzania and Zambia guidelines recommended testing for CD4 + < / ≤ 200 cells/mm^3. The Mozambique guidelines recommended testing if additional criteria are met, including danger signs or suspicion of cryptococcal disease, or WHO stage 3 or 4 disease.

Tuberculosis

In line with the WHO, all national guidelines recommended screening for TB. The use of urine lipoarabinomannan (LAM) testing to screen for tuberculosis was discussed in all national guidelines except those from Ivory Coast. Only the Ghanaian and Ethiopian guidelines separated the targeted population by in- and out-patient as per WHO 2021 guidance (inpatient: ≤ 200 cells/mm^3, outpatient ≤ 100 cells/mm^3, or any CD4 count with symptoms or if seriously ill). All guidelines recommended the use of urine LAM in patients who are severely ill or have danger signs, independently of CD4 count.

Prophylaxis for opportunistic infections

Cotrimoxazole

All national guidelines recommended cotrimoxazole (CTX) prophylaxis but there were differences in the criteria for timing of initiation and discontinuation. According to the WHO 2021 guidance, CTX should be provided to all PHW with a CD4 cell count of less than 350 cells/mm^3 or clinical stage 3 or 4 disease, or in settings with high prevalence of malaria or severe bacterial infection. The Zambian guidelines recommended starting CTX if the CD4 counts is < 350 cells/mm^3 or with clinical stage 3 or 4 disease. Ivory Coast and Republic of Congo guidelines recommended starting CTX in all PWH irrespective of the CD4 count, based on the high prevalence of malaria or severe bacterial infections. Mozambique guidelines expanded the use of CTX to also include patients with WHO clinical stage 2. Ethiopia, Ghana, Tanzania, and Rwanda guidelines recommended CTX for all PWH with active tuberculosis regardless the level of CD4, with differences in other indications. Except the use of CTX in patients with tuberculosis, guidelines of Ghana

Table 2 Agreement of country specific guidelines to WHO 2021

	WHO 2021	Ethiopia	Ghana	Ivory Coast	Mozambique	Republic of Congo	Rwanda	Tanzania	Zambia
Definition of AHD									
Definition	Reference								
Screening									
CD4 testing at baseline	Reference								
Cryptococcal antigen	Reference								
- **Population group**	Reference								
Routine TB screening	Reference								
- **Urine LAM**	Reference								
○ **Population group**	Reference								
Prophylaxis									
Cotrimoxazole	Reference								
- **Population group**	Reference								
- **discontinuation**	Reference								
Pre-emptive therapy for cryptococcal antigenemia	Reference								
TB preventive therapy	Reference								
- **Population group**	Reference								
Supportive care									
Specified adherence information	Reference								
HIV treatment									
Recommended 1st line ART	Reference								
Delayed/Deferred ART start after start of TB/cryptococcal treatment									
- **TB at non-neurological site**	Reference								
- **TB meningitis**	Reference								
- **Cryptococcal meningitis**	Reference								
AGREEMENT		16	15	7	13	14	13	13	12
PARTIAL AGREEMENT		2	3	0	4	1	2	3	3
NO AGREEMENT		0	0	3	1	1	2	1	2
NOT ADDRESSED		0	0	8	0	2	1	1	1

AHD advanced HIV Disease

ART anti retroviral therapy

LAM lipoarabinomannan

Table 3 Index of national guidelines

Country	Name	References
Ethiopia	National Guidelines for Comprehensive HIV Prevention, Care and Treatment	[13]
Ghana	Consolidated Guidelines for HIV Care in Ghana	[14]
Ivory Coast	Directives 2019 de prévention et de prise en charge de personnes vivant avec le VIH en Côte D'Ivoire	[15]
Mozambique	Guião de cuidados do HIV do Adulto, Adolescente Grávida, Lactante e Criança	[16]
Republic of Congo	Lignes directrices relatives à l'utilisation de médicaments antirétroviraux pour le traitement et la prévention de l'infection à VIH au Congo	[17]
Rwanda	Guidelines for HIV Prevention, Treatment and Care in Rwanda	[18]
Tanzania	National Guidelines for the Management of HIV and AIDS	[19]
Zambia	Zambia Consolidated Guidelines for Treatment and Prevention of HIV Infection	[20]

recommended CTX in line with the WHO 2021; Rwanda guidelines considered virologic failure (HIV RNA > 200 copies/ml) as a criterion for treatment; Ethiopian and Tanzania guidelines did not provide additional clinical criteria for initiating CTX prophylaxis.

All guidelines except those from Rwanda provided guidance for discontinuation of CTX for PWH. The WHO 2021 stated that CTX can be stopped if a patient is stable on ART with immune recovery or viral suppression. Guidelines from Ghana, and Tanzania aligned with the WHO guidance. In settings with a high burden of malaria or severe bacterial infections, CTX should be continued regardless of CD4 count or clinical stage, which is recommended in the guidelines of the Republic of Congo. Ethiopian guidelines include an option to discontinue prophylaxis with combining HIV viral load testing and CD4 testing. All other national guidelines recommended discontinuing CTX prophylaxis based on CD4 counts.

Cryptococcal antigenemia and tuberculosis preventive therapy

Other than the guideline of Ivory Coast, which do not address this item, all guidelines recommended pre-emptive therapy for cryptococcal antigenemia. All national guidelines recommended tuberculosis preventive therapy for all PWH.

Supportive care interventions

The Guidelines of Ivory Coast and Tanzania did not provide any information about supportive care interventions. Recommendations for adherence for people with AHD from the other countries included measures such as home visits or specific communications interventions.

Antiretroviral therapy

Regimen

The recommended first-line ART regimen for all countries was in line with the WHO guideline: Dolutegravir (DTG)/ lamivudine (3TC)/ tenofovir disoproxil fumarate (TDF) or DTG/emtricitabine (FTC)/TDF.

Timing of ART initiation in the presence of opportunistic infections

Non-neurological TB The WHO guidelines recommend starting ART within 2 weeks for PWH with tuberculosis at a non-neurological site, independent of CD4 cell count. Guidelines from Ethiopia, the Republic of Congo, Mozambique, and Tanzania provided the same recommendation; Zambian guidelines recommend a start within ten days. Ivory Coast guidelines recommended deferring ART initiation for 2 weeks. Rwandan guidelines took a similar approach but suggested starting ART within 4–6 weeks for CD4 counts above 50 cells/mm^3. Ghana guidelines recommended to start ART as soon as possible and within two weeks if practicable but latest after 8 weeks and initiation should be deferred if clinical symptoms suggest meningitis.

Tuberculous meningitis (TBM) WHO 2021 guidelines recommend delaying start of ART for 4–8 weeks for patients with TBM. Ethiopian guidelines provided the same information. Guidelines from Ghana, and Mozambique recommended slightly different timings for ART initiation, but were similar to WHO recommendations. The guideline of Ivory Coast would start as early as 4 weeks, Rwanda and Zambia within 4–6 weeks. The guidelines of the Republic of Congo did not specify any timing. Tanzania guideline stated to start ART as soon as possible and within 2 weeks after TB treatment.

Cryptococcal meningitis Guidelines from Ethiopia, Ghana, Mozambique, and Rwanda recommended deferring start of ART for 4–6 weeks for people with cryptococcal disease, which is consistent with the WHO 2021 guidelines. Tanzania's guideline recommended deferral for 5 weeks (considered as agreement). The Zambian guideline recommended deferral of ART but do not specify any time period. The Republic of Congo guideline did not provide a clear timeline and the guideline from Ivory Coast did not address this issue.

Overall agreement

Overall agreement for all assessed items (total 18) ranged from 7.0 for the Ivory Coast guideline to 17.0 for the guidelines from Ethiopia (Fig. 1). None of the national guidelines had more than three items not in agreement with the WHO guidelines, and the maximum number of items not addressed by any one guideline was eight. Except the guideline of Ivory Coast (overall agreement: 7.0), all documents showed similar overall agreement (range: 13.5–17.0), irrespectively of publication date (Fig. 2).

Discussion

We evaluated the agreement between the national guidelines of eight sub-Saharan countries participating in the REVIVE trial with the latest WHO guidelines for the management of AHD. Disagreements were minor and mostly due to not covering guideline items. Those deviating from WHO recommendations were confined to recommendations for the target patient population for urine LAM testing, the timing of initiation and discontinuation of cotrimoxazole prophylaxis and the start of antiretroviral therapy in presence of tuberculosis. Except for Ivory Coast, all guidelines addressed most items included in

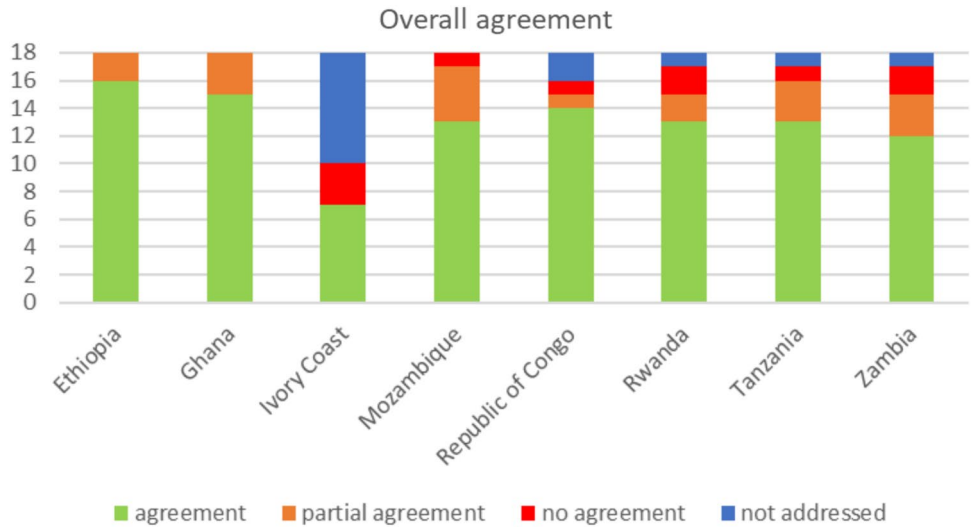

Fig. 1 Overall agreement by country

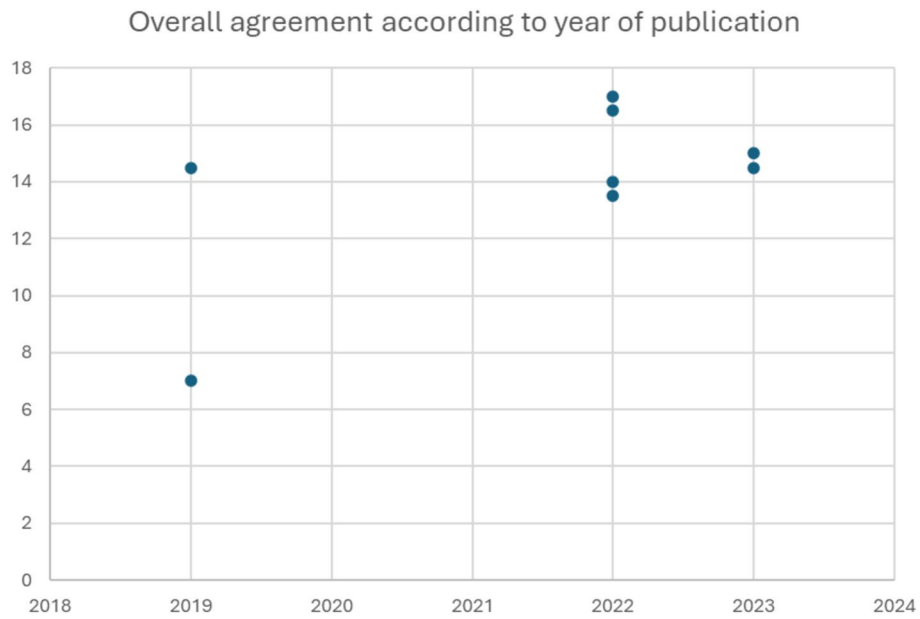

Fig. 2 Overall agreement according to year of publication

the WHO guidance, highlighting the comprehensive nature of the national AHD guidelines. Compared with our previous report that evaluated the six vanguard countries participating in REVIVE, the current review shows less disagreement for the different indications for deferred ART [12].

All 14 countries participating in the REVIVE trial (six in the previous and eight in the current review) have their own national guideline, and any substantive differences from the WHO guidelines appear to reflect country-specific considerations, such as burden of malaria for CTX prophylaxis or available resources. The importance of local context to implement the WHO guidelines is highlighted in the WHO 2017 document [2].

All national guidelines were published after the first WHO document addressing AHD management in 2017 [2], and only the Tanzania and Ivory Coast guidelines were published before the comparator for this review (WHO 2021) [12]. However, all guidelines–except Ivory Coast–showed high agreement, irrespectively of

the publication date. This is in contrast to our previous report, indicating a trend towards a higher agreement score over time.

The first step of managing AHD is to identify the patient population based on universally accepted definition. Correlation of CD4 count < 200 cells/mm^3 with the WHO clinical stage criteria for advanced HIV (stage 3 and 4) is poor [21–23]. For instance, people with a CD4 count of < 100 cells/mm^3 may present without stage 3 or 4 disease, and therefore reliance on clinical staging alone may fail to identify those at highest risk [7]. All national guidelines recommended CD4 testing for PWH entering or re-entering care, as this enables clinicians to identify AHD even in asymptomatic individuals. If CD4 testing is not available, some guidelines emphasized the use of WHO clinical stage assessment. A recently published WHO policy brief addressing the management of opportunistic infections in AHD supports CD4 testing to detect AHD and determine eligibility for CTX prophylaxis [24]. Ehrenkranz *and colleagues* highlight the importance of CD4 testing for risk stratification, in the context of declining use of routine testing based on the perception by funders that routine testing has limited cost effectiveness [25]. As a consequence of reduced donor and governmental funding support for CD4 testing, some manufacturers are withdrawing quantitative CD4 testing devices from the market [26].

Based on the WHO clinical stage classification, people with pulmonary tuberculosis or extra-pulmonary tuberculosis are defined as having stage 3 or 4 disease and are therefore considered to have AHD [27]. The WHO guideline recommends starting cotrimoxazole in all patients with a CD4 cell count of < 350 cells/mm^3 or clinical stage 3 or 4 disease. The national guidelines of three countries separately recommend the use of CTX in people with active tuberculosis; this is likely based on a randomised trial performed in the Ivory Coast before ART was widely available showing reduction in mortality and hospital admission with this approach [28].

In our previous report we found that none of the six national guidelines provided different CD4 cut offs for Urine LAM testing for inpatients and outpatients [11]. In the current report, two national guidelines provided such guidance.

According to WHO, ART should be started within seven days of HIV diagnosis except for those also diagnosed with cryptococcal meningitis or tuberculous meningitis [12]. Both these infections are important drivers of mortality in PWH [8, 29], and immediate ART initiation is associated with harm [12, 30]. Some national guidelines still retain specific recommendations for ART timing among people with non-neurological TB, based on CD4 thresholds. Only one guideline was in exact agreement with the WHO 2021 guideline regarding the deferral of ART in presence of TB meningitis.

In summary we found that national guidelines for the management of AHD from eight countries in sub-Saharan Africa with a total population of more than 300 million people have a high level of agreement with the most recently updated 2021 WHO guidelines.

Abbreviations

3TC	Lamivudine
AHD	Advanced HIV disease
ART	Antiretroviral therapy
CTX	Cotrimoxazole
CD4	Cluster of differentiation 4
DTG	Dolutegravir
FTC	Emtricitabine
HIV	Human immunodeficiency virus
LAM	Lipoarabinomannan
PWH	People living with HIV
TB	Tuberculosis
TBM	Tuberculous meningitis
TDF	Tenofovir disoproxil fumarate
WHO	World Health Organization

Author contributions

TCS, SW, JWE, DM, GM designed the research project and performed data extraction. TCS, JWE, SW, DM, GM analyzed the data and drafted the manuscript. TBF, TF, YH, AM, RM, AD, LC, FN, CK, LB, OS, MMi, KN, MMu and SR assisted in data acquisition and revised the manuscript and provided interpretation. All authors approve the submission of the final draft of the manuscript.

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Availability of data and materials

Data is provided within the manuscript.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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