REPORT FROM THE

SCOPING CONSULTATION ON SEVERE BACTERIAL INFECTIONS AMONG PEOPLE WITH ADVANCED HIV DISEASE

VIRTUAL MEETING
23 NOVEMBER 2021

World Health Organization

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CONTENTS

LIST OF ABBREVIATIONS

ART	antiretroviral therapy
CD4	cluster of differentiation 4 (cell surface protein subtype for lymphocytes)
FIND	Foundation for Innovative New Diagnostics
TB	tuberculosis

1. INTRODUCTION

1.1 Objectives

This meeting aimed to explore future directions for developing WHO guidance on severe bacterial infections by identifying key challenges and knowledge gaps.

The following key points were addressed:

- reviewing the current evidence on using prophylactic antibiotics (specifically azithromycin and other macrolides) as part of the advanced HIV disease package of care;
- reviewing options for preventing severe bacterial infections in the context of antimicrobial stewardship;
- current opportunities for diagnosing severe bacterial infections; and
- research gaps and implementation challenges.

1.2 Participants

The participants included HIV programme managers, experts in HIV, infectious diseases, antimicrobial resistance, principal investigators of key research studies, representatives of civil society, implementation partners and donors. The participants were from India, Italy, Kenya, Malawi, Malaysia, Philippines, South Africa, Switzerland, Thailand, Tunisia, Uganda, the United Kingdom of Great Britain and Northern Ireland, the United States of America (USA), Zambia, and Zimbabwe. In accordance with WHO policy, declaration of interests' forms, and confidentiality agreements were obtained from all participants before the meeting.

1.3 Background

Despite major improvements in access to HIV testing and treatment, about 680 000 people die each year from HIV-associated causes *(1)*. Individuals with advanced HIV disease have greatly compromised immune status and are highly susceptible to opportunistic infections such as tuberculosis (TB), cryptococcal meningitis, severe bacterial infections and a host of other infectious diseases including histoplasmosis, talaromycosis, cytomegalovirus infections and, more recently, severe COVID-19 *(2)*. Although the median CD4 cell count of individuals initiating antiretroviral therapy (ART) has improved over time, the proportion of individuals with advanced HIV disease when initiating ART remains at about 30% *(3)* in many regions of the world, including high-income countries, with men presenting more frequently with advanced HIV disease than women *(4)*. Further, advanced HIV disease is increasingly prevalent among individuals who have initiated ART and subsequently disengaged from care *(5)*. Several countries have made significant progress in terms of high volumes of HIV testing and subsequently lower rates of advanced HIV disease, such as Botswana, Rwanda, and Cuba *(6)*. Nevertheless, reducing advanced HIV disease incidence and improving the identification of people at risk of disease progression is of paramount importance, especially to end excess individual suffering and achieve global targets to end AIDS as a public health threat and reduce the number of people dying from AIDS-related causes *(7,8)*.

WHO currently recommends a package of care for advanced HIV disease *(9,10)* that includes rapid initiation of ART, preventive therapy against TB, prophylaxis, or pre-emptive treatment for cryptococcal meningitis and co-trimoxazole prophylaxis. This care package includes systematic screening for TB, cryptococcal antigen testing and enhanced adherence counselling. CD4 cell count is the preferred way to diagnose advanced HIV disease. Although this package covers some of the common causes of illness and death, the characterization of and response to severe bacterial infections, including diagnosis, prevention, and management, has presented a significant challenge for public health programmes.

Azithromycin has been evaluated as part of the advanced HIV disease package of care, and there has been increased interest in the potential role for this antibiotic as a candidate for mass drug administration or prophylaxis *(11,12)*. Although azithromycin was not included as part of the WHO-recommended advanced HIV disease package, WHO has recently issued recommendations endorsing the use of azithromycin as mass prophylaxis for children younger than five years in settings with high mortality; this recommendation is not specific to HIV and was made after weighing the various risks, which include the development of antimicrobial resistance *(12,13)*. When azithromycin use is being considered among adults and adolescents with advanced HIV disease, further concerns include increases in antibiotic-resistant sexually transmitted infections, notably azithromycin-resistant gonococcal infections. Recent reports from the WHO global antimicrobial resistance surveillance for Neisseria gonorrhoeae report that, between 2017 and 2018, 84% of countries that reported on gonococcal resistance (51 of 61) reported antimicrobial resistance to azithromycin *(14)*. Another concerning development has been the emergence of extensively drug-resistant Salmonella typhi, for which azithromycin is among the last available antibiotics *(15)*.

Despite these, there remains a need to reconsider diagnostic, therapeutic and prophylactic approaches that could be included in the advanced HIV disease package to help further reduce mortality.

2. SUMMARY OF MEETING DISCUSSIONS

2.1 Introduction and meeting format

This meeting consisted of two parts. Part 1 addressed the use of antibacterial drugs in the context of severe bacterial infections in advanced HIV disease, and part 2 addressed approaches for managing severe bacterial infections, key knowledge gaps and implementation questions in relation to the advanced HIV disease package of care. Each part comprised several presentations from subject matter experts, followed by a facilitated discussion. The first part enabled discussion specifically on azithromycin and other macrolides that have been considered for prophylaxis in the past and are also used as a preventive measure among children. The second part enabled discussion on emerging diagnostics, considerations around their use in low- and middle-income countries and the timelines for developing technologies.

To support the meeting discussions, it was important to understand the current knowledge around severe bacterial infections, including updates from the key clinical trials that informed the development of WHO guidance on advanced HIV disease, an overview of data relating to severe bacterial infections, knowledge sharing from other WHO consultations relating to severe bacterial infections, experience on developing recommendations for mass prophylaxis with azithromycin in other contexts and the importance of weighing risks and benefits in the context of rapidly emergent antimicrobial-resistant organisms. Two expert panels were organized to ensure a detailed discussion of the topics by the group, facilitated by two co-chairs.

2.2 Key challenges with severe bacterial infections

There is in general very limited access in low- and middle-income countries to reliable microbiology diagnostic tools, including blood cultures, and relatively poor assessment of the prevalence of drug-resistant organisms. Consequently, clinical diagnosis is the key tool for screening for severe illness. Azithromycin administration is recommended in some country guidelines for people who are severely ill. Representatives of civil society stated that urgent action is needed to respond to the challenges that severe bacterial infections pose considering the need to make progress since the introduction of the WHO package of care for HIV in 2017 *(9)*.

One key challenge is the limited access to either point-of-care or lab-based CD4 cell count tests, which creates difficulty in identifying who has advanced HIV disease. Recent reports suggest that the advanced HIV disease population increasingly includes individuals who have disengaged from care and re-engage with care with advanced HIV disease when clinically unwell.

The REALITY trial reported that offering a package of care reduced mortality among individuals with advanced HIV disease, but overall, the actual causes of death were often multifactorial and presented difficulties in ascertainment, since many of these individuals died at home. A subsequent sub study helped rule out cryptococcal disease as a major cause of death through retroactive testing for cryptococcal antigen from lab samples *(11,16,17)*. The specific causes of death are often difficult to identify and include severe bacterial infections, TB and invasive fungal or viral infections. The REALITY investigators suggested that low CD4 cell count predicted mortality from unknown causes and cryptococcosis; other predictors such as fever and metabolic derangements could be explained in part by undiagnosed TB and atypical mycobacteria. This is important, since in many settings the diagnosis of TB is often delayed, with limited access to diagnostic tests, including lateral flow urine lipoarabinomannan assay test, which is a preferred rapid test to detect TB in addition to a WHO-recommended molecular test (such as Xpert® MTB/RIF). This is further complicated by difficulties in obtaining appropriate samples for testing for some individuals, such as individuals who produce very little sputum despite having TB. Better identification of TB and rapid linkage to care is needed, reinforcing the recommendation to ensure diagnostic integration in HIV and TB programmes *(18)*.

The meeting participants agreed that co-trimoxazole still has a definite role in preventive prophylaxis. Despite the increased likelihood of antimicrobial resistance from long-term use, co-trimoxazole still has an important role in preventing *Pneumocystis jirovecii* pneumonia, community-acquired pneumonia, and *Salmonella* and *Isospora* infections. Meeting participants also determined that a subgroup-based approach may be warranted when considering additional antibacterial prophylaxis, considering the relative susceptibility to serious infections, but further assessment is needed to decide what CD4 cut-off would be appropriate to inform specific guidance (such as a CD4 cell count ≤50 cells/mm^3).

2.3 Severe illness, bacterial infections, and HIV

The meeting participants agreed that it is important to examine the issue of severe bacterial infections in terms of patient subpopulations – outpatients and hospitalized patients – since each of these populations has a different set of needs and different risks of mortality and morbidity.

For the management of an individual presenting with an acute febrile illness, knowledge of HIV status is a key aetiological triage. This will both inform the subsequent clinical actions and establish severity. Prophylactic antibiotics do not have a role in this context, and an adequate response would need broad-spectrum antibiotics administered intravenously, critical care protocols and approaches to managing sepsis. Meeting participants noted that disseminated TB is a distinct entity among seriously ill individuals with HIV and strongly emphasized the need to establish a diagnosis of TB and consider empirical TB treatment if there is sufficient clinical suspicion. Autopsy studies suggest that, in many instances, people who are serioulsy ill and with advanced HIV have polymicrobial infections advanced HIV disease have polymicrobial infections *(19)*, with TB as a frequent cause. There is no guidance on the use of step-up and step-down of broad-spectrum antibiotics among people seriously ill with advanced HIV disease. Managing hospitalized people with advanced HIV disease with sepsis in low- and middle-income countries thus emerged as an important focus. Many people do not receive a blood culture before antibiotic therapy, which makes escalation of antimicrobial therapy less precise and will likely result in increased antimicrobial resistance (South Africa being a notable exception, where timely blood cultures are feasible). Evidence from the REALITY trial showed that most deaths occurred within the first four weeks, underscoring the need for timely interventions *(17)*.

2.4 Diagnostics for severe bacterial infections

A recent report by FIND on the landscape for emerging diagnostics highlighted several emerging novel diagnostics, with many currently unavailable in low- and middle-income countries. It was noted that the timeline for their development is relatively short (5–6 years), but feasibility and cost–effectiveness would need to be assessed. Some key points of agreement among meeting participants were that any new severe bacterial infection diagnostic tool should include broad-based identification of bacterial pathogens and markers for antimicrobial resistance, require easily accessible clinical samples and be available for use across age groups, since this could improve prognosis and reduce mortality. Identifying what samples are needed and how they are collected (such as respiratory or blood samples) are important considerations.

The importance of continued efforts to diagnose non-bacterial infections – fungal, viral, and parasitic infections – is critical. When feasible, including antibiotic susceptibility testing as part of the diagnostic pathway is valuable. Training needs for the workforce, laboratory requirements and the overall set-up and running costs and models of implementation all require planning. Diagnostics that yield non-specific markers of disease (such as erythrocyte sedimentation rate or C-reactive protein) are less likely to be useful, since they offer only marginal improvements on clinical assessment and examination, except for C-reactive protein, when used as part of an algorithm to screen for TB, in accordance with recent WHO screening guidelines *(20)*.

Currently available bacterial testing systems have slow turnaround times in the context of needs for sepsis management – taking days instead of hours – and few commercially available devices currently use whole blood to identify bacterial pathogens, with cultures and isolates still being required for antibiotic susceptibility testing. Several testing systems are in the diagnostics pipeline that will use whole-blood samples, but assessment of their performance is not available at this time. Cost considerations are a potentially important barrier, with relatively high anticipated costs per test. As these technologies achieve economies of scale, costs will likely decline and cost–effectiveness assessments will provide further insight.

There is a clear need to make these technologies available in low- and middle-income countries to ensure equity, since many of these countries bear the greatest burden of both advanced HIV disease and severe bacterial infections. Currently, there is no ideal test for sepsis for use in low- and middle-income countries. There remain significant challenges in the availability of antibiotic susceptibility testing in terms of the desired time frame of results in any setting, and very few platforms exist that offer simplicity of technology for use in primary and secondary settings. Many of these technologies should be made available at all levels of health-care systems, which requires a health systems approach to adopting these technologies.

2.5 Experience with mass prophylaxis

Azithromycin has been used as mass prophylaxis, primarily among children. The TANA (Trachoma Amelioration in Northern Amhara) trial in the United Republic of Tanzania in 2009 *(21)* demonstrated nearly 50% mortality reduction among children 1–9 years old. More recently, the MORDOR (Macrolides Oraux pour Réduire les Décès avec un Oeil sur la Résistance) trial in Malawi, Niger and the United Republic of Tanzania found a 13.5% reduction in mortality overall, although the individual country analysis found a significant reduction in mortality only in Niger *(12,22)*. Preventing bacterial infections has been considered in the past among people living with HIV with the use of azithromycin prophylaxis against Mycobacterium avium complex infection among individuals with CD4 counts <50 cells/mm3, but this indication has recently been removed from some clinical guidelines *(23)*.

Current WHO guidelines recommend against using azithromycin as mass prophylaxis among children, except in settings where child mortality is high and antibiotic resistance can be monitored *(13)*. Key issues discussed by the WHO guideline development group for this guideline related to antimicrobial resistance and ethics around using mass drug administration. Although the development of drug resistance is known for azithromycin, one key ethical issue was why countries with poor access to high-quality health services, including antimicrobial agents, and high mortality from childhood disease should relinquish the use of an antibiotic that may potentially prevent deaths now to guard against future possible drug resistance. Further, several meeting participants noted that azithromycin may cause long-QT syndrome. This condition is considered to be rare, with no differences in risk among children and adults *(24)*. These considerations, in addition to the positive results from the MORDOR trial, led to the development of two WHO guidelines recommending its use in low- and middle-income countries to prevent childhood illness, considering epidemiology and context.

Trial data suggest that co-trimoxazole could have preventive activity against pneumococcal disease *(25)*. Further, the clinical status of an individual with advanced HIV disease is important to consider for using preventive measures, since azithromycin prophylaxis would have a limited role for individuals who already have sepsis or who are seriously ill.

The meeting participants raised several important issues.

- Azithromycin use by individuals with advanced HIV disease need not be viewed as mass drug administration since it pertains to a specific subset of individuals at increased risk of mortality.
- A detailed assessment of antimicrobial resistance and epidemiology is needed before considering azithromycin for people with advanced HIV disease.
- A clear assessment of risks and benefits is necessary and developing estimates of burden of severe bacterial infections or disease modelling of antimicrobial resistance is key to informing any development of guidance.
- There is a potential risk of increased drug resistance in microorganisms with limited therapeutic options – such as gonococcal and *Salmonella* infections.
- A better understanding is needed of side-effect profile among adults such as long QT-interval syndrome, particularly in the context of polypharmacy for individuals with advanced HIV disease.
- Further options need to be considered for preventing severe bacterial infections among children since children living with HIV have significant burden from bacterial respiratory disease.
- The current evidence on the use of pneumococcal vaccination among adults living with HIV need to be reviewed, since pneumococcal infections have been known to cause significant mortality in advanced HIV disease.

Azithromycin has also seen increased empirical use as a supportive treatment during the ongoing COVID-19 crisis in low- and middle-income countries, such as in India *(26)*. The impact of this broad use, despite limited rationale and benefit *(27)*, has yet to be assessed.

2.6 Emergent drug resistance

The development of antimicrobial resistance could be a serious unintended consequence of azithromycin use. Better antimicrobial resistance surveillance data are generally needed, and any programme that involves azithromycin needs to monitor for antimicrobial resistance. Better understanding of the extent to which genetic resistance determinants correlate with phenotypic resistance is also clearly needed. Combining phenotypic and genomic approaches to monitor changes in antimicrobial resistance may be useful but is currently challenging in low-income settings. A better understanding of the impact of azithromycin on the spread of extended spectrum beta-lactamase resistance bacteria and community-associated methicillin-resistant *Staphylococcus* aureus infections is important, and further insights into the long-term impact on the microbiome and its potential consequences are needed. Further, increased resistance has been noted in *Salmonella* (typhoidal and non-typhoidal) and in *Shigella* spp. *(28–31)*. Some HIV-negative populations such as individuals with cystic fibrosis have shown low rates of resistance development with azithromycin *(32)*, but the evidence is limited.

Targeting delivery of azithromycin to those at high risk of death might optimize benefit while minimizing antibiotic exposure but is best supported through disease modelling to estimate long-term effects, a view that meeting participants broadly supported. Several experts noted that the predicted absolute mortality risk–benefit ratio would be a key factor to decide in which setting the drug may be used to develop recommendations. Future research to evaluate the use of azithromycin should include individuals initiating ART, those re-entering care and children. A consultative approach should be taken to help to develop and design such research. Other questions posed include the assessment of dose response and emergence of resistance to establish the dosing and frequency of azithromycin, since there is currently limited evidence to determine the appropriate length of a prophylactic regimen. The timing of offering of azithromycin is another knowledge gap. A need was identified to develop clear protocols to step up and step-down antimicrobial treatment among individuals with advanced HIV disease who were hospitalized.

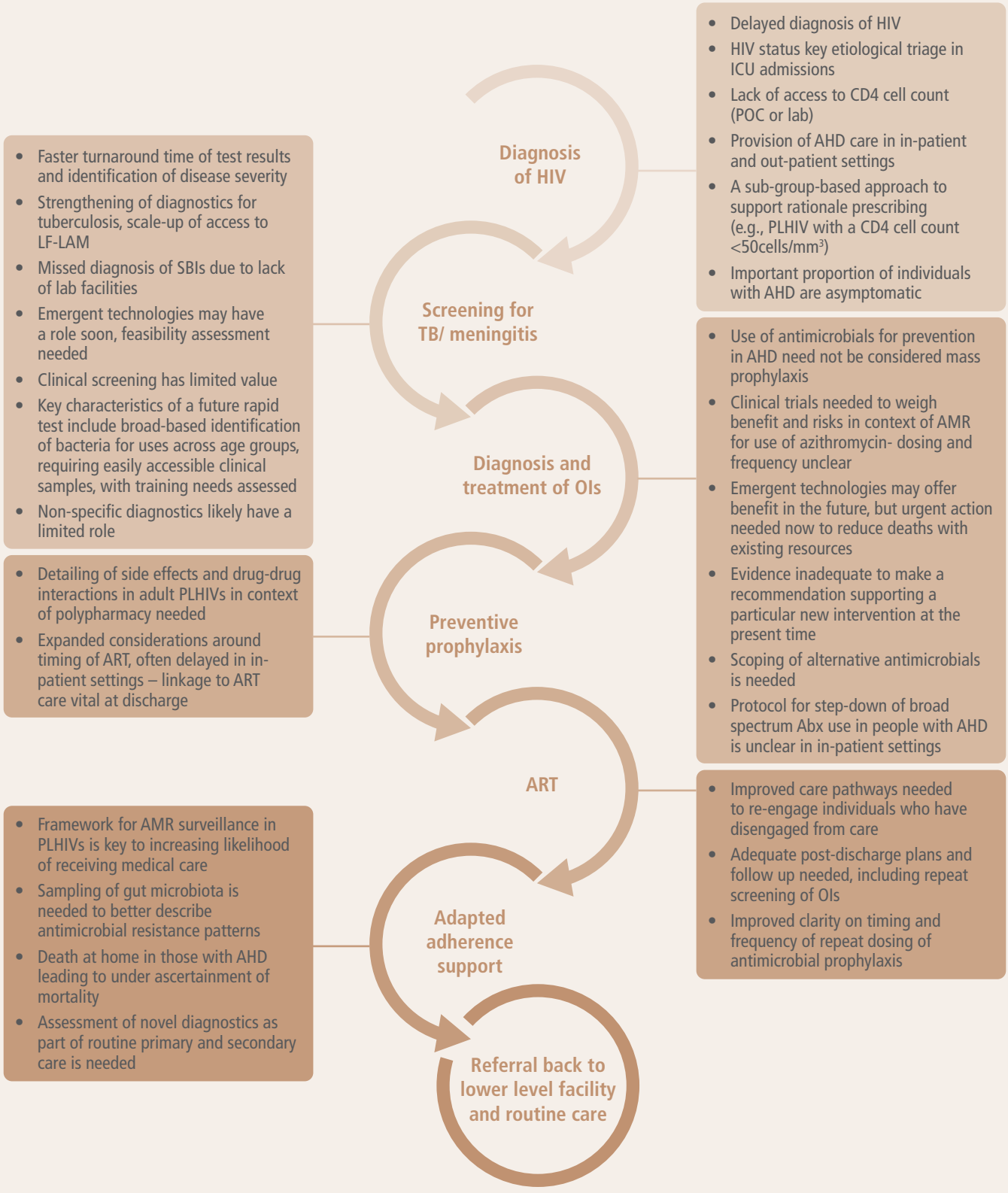
3. KEY MEETING OUTCOMES

Meeting participants agreed on the following key issues.

- Severe bacterial infections are a priority issue among individuals with advanced HIV disease, and their management is a key component to ending AIDS-related deaths by 2030.
- Severe bacterial infections consist of a challenging group of pathogens that affect those with advanced HIV disease in both outpatient and inpatient settings; therefore, developing tiered guidance is critical.
- In the short term, implementation research can develop accurate estimates of severe bacterial infections and antimicrobial resistance surveillance.
- An important and urgent call is for specific studies that document cause of death and premature death among people living with HIV to help understanding of how bacterial, viral, and fungal infections and other causes are implicated in advanced HIV disease mortality.
- Guidance needs to be developed for managing severe bacterial infections in inpatient settings.
- Better evidence is needed to help inform policymaking on prophylaxis with azithromycin, which may be achieved through:
  - A randomized clinical trial to assess the efficacy of azithromycin among adults, adolescents and children with advanced HIV disease as empirical prophylaxis and assessment of resistance as well as information on azithromycin resistance to targeted pathogens. A trial is best equipped to provide information on absolute risk reduction of mortality to provide strong evidence of benefits.
  - Reporting from observational cohorts on advanced HIV disease.
- Despite the need for further evidence around azithromycin, several meeting participants, including those representing the HIV community, reinforced the need to act rapidly, and that saving lives in the short term is an important priority while awaiting the results of any trial or observational study to report its findings.
- Cost and cost–effectiveness analysis, disease modelling studies assessing emergent drug resistance and feasibility and acceptability assessments of emergent diagnostics technologies in low- and middle-income countries are needed.

Fig. 1 summarizes the key knowledge gaps, consideration put forward by the expert group, as seen through the perspective of the advanced HIV disease care continuum.

Figure 1. Key considerations for SBIs through the AHD care continuum*



[a] See Chapter 4 of the 2021 WHO consolidated guidelines on HIV *(18)* for the full advanced HIV disease algorithm.

4. CONCLUSIONS

Participants of this meeting shared a clear overall vision of addressing SBIs as a priority and also articulated the need for clinical and implementation research as well as cost-effectiveness modelling to provide better insights and offer solutions to countries with a heavy burden of SBIs.

WHO is committed to leveraging its ability to convene key stakeholders to organise a public health response to SBIs alongside the AHD package of care to target other key causes of mortality and morbidity, such as HIV-associated TB, cryptococcal disease, histoplasmosis and other opportunistic infections.

WHO will support the continuation of technical dialogue on this topic to deliver country-level impact.

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ANNEX 1. FINAL MEETING AGENDA

Topic:
WHO Scoping consultation on Severe Bacterial Infections in Advanced HIV disease

Time:
Nov 23, 2021 03:00 PM Zurich (CET)

Final meeting agenda

Time	Topic	Speakers
10 minutes	Introductory remarks and introductions	Meg Doherty and Marc Mendelson (co-chairs)
10 minutes	Overview of advanced HIV disease	Graeme Meintjes
10 minutes	What do we know about severe bacterial infections? Overview of current issues and key considerations	Ajay Rangaraj
Part 1: Addressing the use of antibacterial use in the context of severe bacterial infections in advanced HIV disease		
10 minutes	Azithromycin mass prophylaxis: WHO guidance	Ayesha Da Costa
10 minutes	Key considerations for antimicrobial resistance	Silvia Bertagnolio
5 minutes	Severe bacterial infections, antimicrobial prophylaxis, and HIV among children	Martina Penazzato
5 minutes	Q & A	
40 minutes	**Facilitated discussion** Guiding questions to the group: • Should antibacterial prophylaxis (other than co-trimoxazole) be considered for adults with advanced HIV disease? • Are macrolides the only candidate for use? • Is azithromycin an appropriate choice in the context of emerging drug resistance? • When is using azithromycin appropriate? • What are the alternatives? • What are the key research questions to guide choice of antimicrobial agent?	**Session chair:** Adeeba Kamarulzaman **Panellists:** Diana Gibb Sanjay Pujari Solange Alves Imelda Mahaka
5 minutes	Break	
Part 2: Approaches to management of severe bacterial infections, key knowledge gaps and implementation questions in relation to the advanced HIV disease package of care		
15 minutes	Diagnostics – status update and current landscape (10 minutes) Q & A (5 minutes)	Sergio Carmona
20 minutes	Panel discussion Diagnostics or empirical management approaches? Feasibility and implementation considerations Community perspectives	Session chair: Marc Mendelson Panel discussion: Sergio Carmona Nicholas Feasey Stephen Watiti
15 minutes	Facilitated discussion	Session chair: Marc Mendelson
10 minutes	Conclusion, next steps and closing remarks	Nathan Ford

ANNEX 2. LIST OF PARTICIPANTS

List of participants

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