REPORT FROM THE

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

VIRTUAL MEETING
23 NOVEMBER 2021

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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

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