HHS Public Access

Author manuscript

Lancet Infect Dis. Author manuscript; available in PMC 2022 January 01.

Published in final edited form as:

Lancet Infect Dis. 2021 January ; 21(1): 16–18. doi:10.1016/S1473-3099(20)30909-9.

Ending deaths from HIV-related cryptococcal meningitis by 2030

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See **Online** for appendix

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The UNAIDS target to reduce HIV-related death to fewer than 500 000 deaths per year by 2020 will not be met.[1] This statement might not be headline grabbing as this target was never as prominent as the 90-90-90 targets,[2] the achievement of which is a necessary but not sufficient step towards ending AIDS mortality.

The decline in HIV-related deaths is too slow. Early initiation of antiretroviral therapy (ART) for people living with HIV is the most important intervention for reducing HIV-related deaths. Access to ART for all is a distant goal in some settings due to ongoing challenges in identifying people with HIV and getting them on to treatment[1] and ART alone isn't enough to fully address HIV-related deaths. Among adults and adolescents, advanced HIV disease is diagnosed as a CD4 count of fewer than 200 cells per μL or a WHO stage 3 or 4 event.[3] Evidence from South Africa shows more advanced HIV disease among ART-experienced people than among ART-naive people.[4] Efforts to prevent disease progression will never replace the need for parallel improvements in the treatment of opportunistic infections.

Gaps exist in current targets and strategies. The 90-90-90 UNAIDS targets, which were endorsed by the UN in 2016, have focused attention on HIV testing and treatment scale-up.[5] Now, as updates to the next global AIDS strategy are being formulated, it is time to introduce ambitious new targets addressing the leading causes of AIDS mortality.

WHO has produced the End TB strategy, which includes targets and indicators for reducing tuberculosis deaths by 90% by 2030.[6] We emphasise the need for a targeted strategy to address HIV-related deaths from cryptococcal meningitis. A similar strategy is also warranted to address serious bacterial infections in people with HIV.

Around 20% of HIV-related deaths in 2014 were thought to have been caused by cryptococcal meningitis.[7] Existing tools and strategies addressing the bulk of this disease burden are hardly implemented and the case for a strategic and targeted approach to address this situation is strong.

The shift from monitoring CD4 cell count to monitoring viral load of ART has contributed to deprioritisation of testing CD4 cell count. Monitoring of viral load and CD4 cell count complement one another and should not be placed in competition. Monitoring viral load supports viral suppression and triage into differentiated care, whereas CD4 cell count identifies people for whom additional intervention is most urgently needed.[3]

Many cases of advanced HIV disease are undiagnosed and few resources are applied even when advanced HIV disease is identified. This scarcity of use results in a low demand for relevant diagnostic, prophylactic, pre-emptive, and therapeutic interventions, in turn contributing to market failure and low levels of access to relevant commodities.[8]

A global strategy should outline steps towards realising the high-level target of ending deaths from cryptococcal meningitis in people living with HIV. Such a strategy should include access to testing for CD4 cell count and cryptococcal antigen for all patients in need, fluconazole and flucytosine in every clinic, and flucytosine and amphotericin B, with laboratories able to support safe administration, in every hospital. Widespread access to this level of care is far from the present reality. The current situation should be viewed by all as unacceptable, as these diagnostics and medicines are essential for patient care.

Flucytosine in combination with amphotericin B for 1 week as induction therapy for cryptococcal meningitis was shown to result in a 24% (27 of 113) mortality at 10 weeks in the ACTA trial,[9] compared with 41% (47 of 114) mortality for amphotericin B with fluconazole for 2 weeks,[9] which is typically used for treatment in the absence of flucytosine. 2 weeks of flucytosine and fluconazole is a safe and effective alternative for settings where amphotericin B cannot be safely administered (eg, where electrolyte monitoring and administration of intravenous infusion might be challenging).[10] The appendix shows the effects of different treatment strategies (appendix p 1). We estimate that around only 1000–2000 of the estimated 162 500 people with HIV-associated cryptococcal meningitis in sub-Saharan Africa[7] were given flucytosine in 2020.

It could take US$15–30 million, depending on acquisition and distribution costs, to provide flucytosine for each of the 180 000 patients with HIV-associated cryptococcal meningitis globally.[7] A strategy that emphasised and prioritised funding gaps could help donors to select priorities that will have the most effect, such as addressing the low use of flucytosine.

Such a strategy should also ensure that national programmes measure ongoing progress by use of simple indicators for cryptococcal meningitis, as is the case for tuberculosis. Beyond having the tools and monitoring their use, strengthening of health systems is needed, particularly training health-care workers on the front line, building laboratory capacity, and ensuring a sustainable procurement and supply chain.

Beyond reducing mortality with existing tools, in the next 5 years there is a need for programmatic innovation and products to close the diagnostic and therapeutic gap in the medium term (ie, 5–10 years). Finally, there should be improvements in clinical care in settings with scarce resources, including for people living with HIV who are admitted to hospital. These suggestions are easy to state and difficult to achieve but necessary if the benefits of new tools are to be realised.[11]

Now is the time for UNAIDS, WHO, national policy makers, and donors to support a comprehensive strategy for ending HIV-related deaths from cryptococcal meningitis by 2030, incorporating this goal into relevant health policies and developing a mortality indicator for HIV-related cryptococcal meningitis. Together with similar efforts to address

deaths from tuberculosis and bacterial infections, such an approach can help to renew global efforts to end all HIV-related deaths by 2030.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

AS reports personal fees from Drugs for Neglected Diseases Initiative and Centers for Disease Control and Prevention Foundation, outside the submitted work. DWD and family hold founder shares in F2G, a University of Manchester spin-out antifungal discovery company. DWD acts or has recently acted as a consultant to Pulmatrix, Pulmocide, Zambon, iCo Therapeutics, Mayne Pharma, Biosergen, Bright Angel Therapeutics, and Metis. In the past 3 years, DWD has been paid for talks on behalf of Dynamiker Biotechnology, Hikma Pharmaceuticals, Gilead Sciences, Merck, Mylan, and Pfizer. DWD is a longstanding member of the Infectious Disease Society of America Aspergillosis Guidelines group, the European Society for Clinical Microbiology, and Infectious Diseases Aspergillosis Guidelines group. TSH reports grants from the UK Medical Research Council, French National Agency for Research on AIDS and Viral Hepatitis, European and Developing Countries Clinical Trials Partnership, and Gilead Sciences; personal fees from Gilead Sciences and Pfizer; and non-financial support from ImmunoMycologics, outside the submitted work. NPG reports grants from the National Institutes of Health, UK Medical Research Council, Bill & Melinda Gates Foundation, Centers for Disease Control and Prevention, and National Health Laboratory Service Research Trust, outside the submitted work. AL reports grants from European and Developing Countries Clinical Trials Partnership, outside the submitted work. RR reports grants from National Institute of Allergy and Infectious Diseases, during the conduct of the study. JNJ reports grants from European and Developing Countries Clinical Trials Partnership, National Institute for Health Research, National Institutes of Health, and UK Medical Research Council, outside the submitted work. All other authors declare no competing interests. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Centers for Disease Control and Prevention.

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