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Ending deaths from HIV-related cryptococcal meningitis by 2030

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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 treatment¹ 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 Africa⁷ 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.

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See Online for appendix

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SARS-CoV-2 and the human-animal interface: outbreaks on mink farms



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On Nov 5, the Ministry of Environment and Food of Denmark announced the culling of all mink in the country, estimated to total approximately 17 million animals.¹ The circulation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had already been observed several months earlier, but the reason for the policy change was an alert from the Danish National Institute of Public Health, which found that viruses had spilled back from mink farms into the community, and that during the passage through mink the virus had accumulated mutations in the spike protein gene.² Spike mutations are scrutinised because the spike is crucial for docking of SARS-CoV-2 to human cells and therefore a key target for vaccines and therapeutic antibodies.³ Preliminary analyses suggested that SARS-CoV-2 isolated from mink in Denmark was less easily neutralised by antibodies in two of nine humans that had been infected with SARS-CoV-2 without the mutations. The effect was small but caused widespread concern in the media, suggesting that the vaccines under development would potentially be rendered useless.² Following review of the evidence, the European Centre for Disease Prevention and

Control and WHO concluded that the risk for the population at large was not increased, but stressed the importance of surveillance at the human–animal interface and rapid exchange of information between virologists and epidemiologists to track possible viral changes that could be of concern.^{4,5} The example of Denmark is a warning: spillover of SARS-CoV-2 from humans to mink and minks to humans is not a new finding. It was first reported in the Netherlands in April, and since has been found in Spain, Italy, the USA, Sweden, and Greece.⁴ In most countries, the first infections on mink farms were identified through contact tracing following confirmation of COVID-19 in symptomatic humans.

Mink belong to the Mustelidae family, which includes ferrets that have been used as an animal model owing to their susceptibility to SARS-CoV-2.⁶ Efficient transmission between ferrets has been shown in experimental infections, with spread to naive animals through direct contact but also through indirect airborne spread.⁷ According to the European Centre for Disease Prevention and Control, Europe has an estimated 2750 mink farms and produces

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