

95/95 BY 2025

ENSURE THAT BY 2025
95% OF PEOPLE WITH
SERIOUS FUNGAL DISEASE
ARE DIAGNOSED AND
95% TREATED = 95-95



Appendix 7

Reduction in AIDS and TB deaths by a million a year, key actions and modelling

90-90-90 + action on fungal diseases will achieve a million more HIV survivors each year by 2020

In 2010, UNAIDS issued the aspirational target of Zero AIDS deaths by 2015. Yet still 1,500,000 people died of AIDS in 2013, a reduction of only 15% from 1,760,000 lives lost in 2010.

At the Global Fungal Infection Forum in Seattle, February 22nd 2015, speakers identified concrete steps to reduce 100,000s of deaths from AIDS annually.

In 2014, the new ambitious target of 90-90-90 was announced with the aim to greatly expand access to diagnosis and ART for all HIV infected patients. This important new target will result in a reduction of HIV transmission and will have some impact on deaths. However, it will take years to achieve the desired outcome of reduced deaths. Progress will be incomplete because coverage will not be 100% and ART reduces the incidence of most co-infections but not all.

Opportunistic infections account for a significant burden of AIDS related morbidity and mortality. For example, about 25% of current AIDS deaths are attributed to tuberculosis (TB). The other 75% are likely to be due to many causes, of which fungal disease is a major contributor, notably *Pneumocystis pneumonia* (PCP), cryptococcal meningitis, disseminated histoplasmosis and chronic pulmonary aspergillosis masquerading as TB. Available evidence suggests that these infections cause about 40% of deaths attributed to AIDS.

Most deaths are a direct result of these diseases with some indirectly linked because of immune reconstitution (IRIS) and drug toxicity, some of which are attributable to unnecessary empirical therapy. Global action to address the current neglect of prevention and treatment of opportunistic fungal diseases that contribute to HIV-related mortality is required to reduce AIDS deaths.

Key actions to reduce deaths

Prevention and treatment of the most common fungal disease is an important concomitant step in preventing AIDS deaths. The following actions, if undertaken widely among high and middle HIV burden countries would have a major impact on survival.

- In recognition of the existing gaps in prevention, two key actions on cryptococcal meningitis diagnosis and treatment have been incorporated within the 2015 WHO guidelines. For example, most LMICs do not have systems for screening for cryptococcal antigen, a critically important intervention. Whilst ARV rollout reduces cryptococcal meningitis rates, serious gaps remain. For example, amphotericin B and/or flucytosine are not available in many countries due to various constraints including lack of registration.



Professor Arunaloke Chakrabarti and Dr M R Shivaprakas on a recent trip to Delhi

1. www.gaffi.org/global-fungal-infection-forum

2. 90-90-90 = 90% of HIV infected patients know their infection status, 90% of all HIV patients receiving ART and 90% viral load suppression.

Reduction in AIDS and TB deaths by a million a year, key actions and modelling

Disease entity	Diagnostic action	Treatment	Proposed action to be taken
Cryptococcal antigenaemia pre-meningitis	Screening <200 CD4	Fluconazole therapy	Promote rapid adoption of 2015 WHO guidelines
Cryptococcal meningitis	Rapid antigen testing (LFA) Lumbar punctures	Amphotericin B + Flucytosine	Promote rapid adoption of 2015 WHO guidelines. Improve access to drugs in high burden countries
<i>Pneumocystis pneumonia</i>	Molecular diagnosis Direct microscopy	Discontinuation of unnecessary empirical therapy. Oral therapy of mild cases	Promote implementation of rapid molecular diagnostic. Develop WHO treatment guidelines
Disseminated histoplasmosis	Antigen (or PCR) testing in relevant countries	Amphotericin B Itraconazole	Ensure access to antigen and/or PCR diagnosis and drugs in high burden countries. Develop WHO treatment guidelines
Chronic pulmonary aspergillosis in 'smear negative TB'	<i>Aspergillus</i> IgG antibody	Itraconazole or amphotericin B	Ensure access to <i>Aspergillus</i> antibody diagnosis and drugs in high burden countries

- *Pneumocystis pneumonia* (PCP) is also a relatively common AIDS-defining illness. It varies in incidence, but is a cause of death in a significant minority of patients sampled at autopsy. Late diagnosis has a worse outcome, and mild cases can be treated with oral therapy as an outpatient, without hospital admission. While the best therapy, co-trimoxazole, is almost universally available, and the WHO has issued guidelines on its use for prophylaxis, there are no WHO guidelines on treatment of PCP. There is a need for clear guidelines including on the use of corticosteroids in treating PCP which are often given, but do not constitute a long-term solution and may reactivate TB. Many molecular diagnostic tests are available but are poorly standardized and too expensive. A low cost diagnostic is required for LMICs. A good candidate, which improves the accuracy of diagnosis and allows diagnosis of mild cases, is in

development. ART rollout is also critical in reducing PCP, and specific guidelines on the diagnosis and treatment of PCP will help improve patient outcomes and reduce preventable deaths.

- Disseminated histoplasmosis is common as an AIDS-defining illness in Central and South America, with mortality ~50%. The rate of disease does not seem to fall with ART rollout, probably because *Histoplasma* is a primary pathogen. Either urinary antigen or blood PCR are excellent early diagnostic tools but they are available in only a few centers. Confusingly, TB is a common concomitant infection. Mortality can be reduced from >50% if based on culture, to <20% with either amphotericin B or itraconazole treatment. Despite its importance in the treatment of histoplasmosis, itraconazole is not on the WHO Essential Medicines List (EML), affecting availability in many countries. Therefore an application

has been submitted to the WHO for itraconazole to be included on the EML. Similar to PCP the WHO has not developed guidelines for the treatment of histoplasmosis; their development will improve diagnosis and treatment and prevent deaths.

- Chronic pulmonary aspergillosis is a relatively common complication of pulmonary TB. Its radiological and clinical manifestations are similar to TB, although fever is uncommon. It is often mistaken for TB, especially smear negative TB. The key diagnostic test, the detection in serum of *Aspergillus* IgG is not widely available in LMICs. Treatment options are amphotericin B or itraconazole, or the newer azoles and echinocandins. ART rollout is unlikely to reduce the incidence of CPA, but reduction in TB cases will.

Modeling of the impact of improved management of fungal disease on AIDS survival

Of the estimated 35 million with HIV infection, 20 million are not on ARVs. Those with CD4 cell counts <100 are at greatest risk of dying, and it is assumed that 2,700,000 people are in this category.

Prior to the institution of the 90-90-90 target, the number of AIDS deaths has been falling at about 80,000 annually, reaching 1,500,000 in 2013. Based on current trends an annual reduction of 450,000-550,000 deaths by 2020 is expected.

90-90-90

Gradual movement towards the 90-90-90 target will likely see a further reduction in deaths. As many of those to be treated will have high CD4 counts and are not at risk of an early AIDS death. So we have estimated an additional 50% deaths per year related to ARVs relative to current declines is estimated. This would add 200,000-250,000 annual survivors.

Cryptococcal disease

The most conservative estimate for AIDS-related cryptococcal meningitis cases worldwide is 372,000 (1). Currently the ten-week survival in treated cases is 30-50%. Since many patients are never diagnosed, it is likely that a minimum of 250,000 AIDS deaths are attributable to cryptococcal meningitis. Screening for cryptococcal antigen and oral treatment with fluconazole (screen and treat) is likely to reduce mortality by 80%. If it is assumed that 60% of cases can be identified by screen and treat and that survival could be increased with the use of amphotericin B and flucytosine to 60% (it is ~85% in Europe and the USA), the minimal survival gain would be 125,000 patients annually. The incidence of cryptococcal infection is likely to fall as 90-90-90 rolls out.

Pneumocystis pneumonia

It is not known how many patients with AIDS develop PCP. A low median

estimate from Thailand was 14.7% (33), among those with <100 CD4 cells, an estimated 400,000. In fact those with CD4 cells between 100 and 200 are also at risk for PCP, so 400,000 is likely to be a low estimate. All patients with PCP who are not treated die. Diagnosis is mostly empirical, but the presentation is often atypical. Assuming that 50% of patients are treated and 70% of them survive currently, the existing annual mortality from PCP is ~260,000. If better diagnosis is instituted, with good clinical guidelines, the diagnosis rate should rise to 80% with only a 20% mortality, saving 120,000 lives annually. The incidence of PCP is likely to fall as 90-90-90 rolls out, yet better diagnosis and treatment in parallel is critical, as breakthrough occurs. There are other arguments for improving the diagnostic approach to PCP (Appendix).

Disseminated histoplasmosis

The number of disseminated histoplasmosis (DH) cases in AIDS has been estimated to be between 100,000 and 300,000. Improved outcomes with early diagnosis and appropriate therapy can achieve 85% survival. The most conservative estimate of annual incidence is 100,000 cases. Assuming that only 20% of patients currently have access to rapid diagnosis, then we would anticipate about 80,000 annual deaths. If antigen and/or PCR were made available to all high incidence communities in the Americas, and both itraconazole and amphotericin B were also used, the survival gain would be 65,000 lives annually.

Chronic pulmonary aspergillosis complicating TB in HIV positive patients

About 1,100,000 patients developed TB in the context of HIV infection in 2013. Of these, 360,000 died and 73% of these deaths occurred in the African region. In all pulmonary TB patients diagnosed

in 2012 with a smear, 1,900,000 of 4,400,000 (43%) were smear negative. In an unpublished study of 39 HIV positive, smear negative patients in Kampala, 26% had detectable *Aspergillus* IgG antibodies and 40% of these patients died within 2 months. Based on their compatible radiology, symptoms and positive serology, it is highly likely these patients suffered from chronic or sub-acute pulmonary aspergillosis (CPA). If we assume that these numbers scale to all HIV positive patients with TB, then 473,000 would be smear negative, 122,000 would have *Aspergillus* IgG antibodies, and 50,000 would die rapidly. Diagnosis and treatment of these patients would prevent ~60% of deaths or 30,000 annually (as well as many more HIV negative people, estimated at 95,000 for prior TB patients only).

Chronic pulmonary aspergillosis complicating TB in HIV negative patients

Of the 7.9 million HIV negative TB cases, 6,715,000 are pulmonary and 5,780,000 survive to one year after diagnosis. Assuming that the estimate of a 5 year period prevalence of 1,052,000 patients previously published (2) is correct and that 15% die annually as 2 recent studies indicated (101,101), the annual mortality is 157,800. Recognising that oral itraconazole is not yet on the WHO EML, and *Aspergillus* antibody testing not available in most LMICs, improvements in survival will accrue slowly, and a 60% improvement would be achieved by 2020. This would reduce current deaths by 94,680 to 63,120.

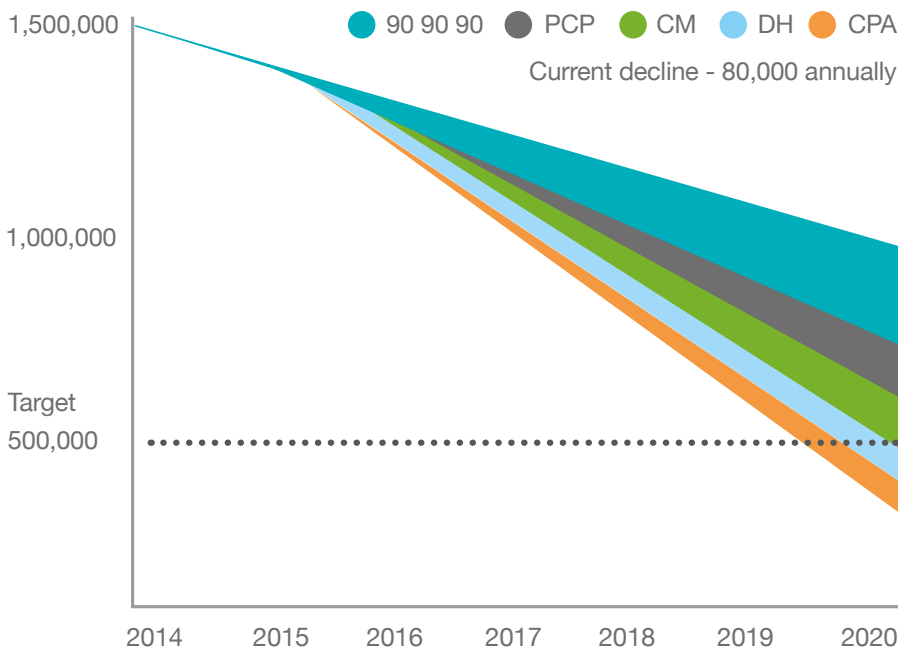
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Conclusions and recommendation

Statistical modeling and limited epidemiological data from clinical settings strongly suggest that the wide adoption of known strategies, current diagnostic tests and antifungal agents for the 4 most common lethal fungal infections in AIDS is likely lead to additional significant reductions in annual HIV deaths, estimated at 700,000 annually. As the true burden of lethal fungal infections is not known, these estimates are conservative. In addition, diagnosis of chronic pulmonary aspergillosis after TB will avoid unnecessary morbidity and reduce deaths by an estimated 95,000 annually.

Nevertheless, evidence suggesting that improvements in diagnosis combined with better and timely availability of safe, efficacious and affordable treatment for fungal disease in HIV care will help reduce HIV deaths is compelling. Depending on implementation and take up, 450,000 deaths might be saved annually. This can be achieved in a manner that avoids duplication of efforts, so excellent value for money, by integrating interventions for fungal disease into existing HIV programs and national strategies and developing treatment guidelines.



Reduction in AIDS deaths to under 1/2 Million by 2020

These estimates are shown graphically in the graph above.



Patients are too often diagnosed with HIV for the first time when they developed cryptococcal meningitis. Greater community sensitization through novel approaches (e.g social media) is needed to bridge this gap.

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The arguments for improving the diagnosis of PCP

Preventing irrational/inappropriate use of corticosteroids and co-trimoxazole

- If the rate of PCP among newly hospitalized adults with advanced HIV infection is 14.7%, then for every 100 admissions, 85 patients will receive high dose co-trimoxazole and probably corticosteroids for 3 weeks unnecessarily. If the actual number of PCP cases is 400,000, then 2.67 million people may be given co-trimoxazole unnecessarily. This translates into 2.4 million nauseated (often vomiting) patients for 3 weeks, 880,000 with a pruritic rash and/or abnormal liver function tests, 1.47 million with neutropenia and 533,000 with a 25% reduction in haemoglobin (especially problematic in women). Nausea will reduce food intake substantially in those who have usually already lost much weight. In addition, co-trimoxazole has been associated with severe erythema multiforme, Steven Johnsons syndrome and toxic epidermal necrolysis, with a very high mortality in LMICs.

Preventing immunosuppression by prolonged unnecessary corticosteroid use

- Assuming that 75% of the patients with PCP are moderate to severe, corticosteroids will usually be given for 21 days, with better outcomes in those with PCP. But corticosteroids have a negative impact on the reactivation and treatment of TB, and lead to higher rates of invasive aspergillosis and progression of chronic pulmonary aspergillosis, as well as probably other opportunistic infections. There are some data suggesting that

corticosteroids may increase survival from pneumococcal pneumonia, also a common infection in HIV patients, but is not studied in HIV patients and may confer no benefit. Using the same assumptions as above, ~2.67 million may be given steroids mostly unnecessarily.

Early detection can help prevent unnecessary hospitalisation and cost

- If 25% of PCP cases are mild, then immediate diagnosis and all oral therapy will potentially avoid 100,000 admissions to hospital, or even more if the diagnosis is ruled out and patients are not admitted for PCP therapy that they don't need.

PCP diagnosis will help prevent misdiagnosis and incorrect treatment for 'TB', and improve patient outcomes

An investigation in smear-negative TB patients identified *P. jirovecii* DNA in sputum in up to 7% in Brazil and 6.7% in Uganda. Investigation of smear-negative TB patients may identify other treatable causes. We have calculated that there are 473,000 smear negative HIV positive TB patients, We can assume that 7% of them have PCP. If we are able to diagnose and treat 70% of them, 23,000 lives will be saved. If some are only colonized by *P. jirovecii* and are not infected as in hospital outpatients in the Camerouns (43%), then this number would come down to 10,000.

UP TO 2.6 MILLION HIV patients admitted to hospital are unnecessarily given high dose cotrim for PCP. With an adverse event rate of 90%, this translates into 2.4 million nauseated and/or vomiting patients, 880,000 with an itchy rash and/or abnormal liver function tests, 1.47 million with a low white blood cell count and 533,000 with anaemia.