World Health Organization

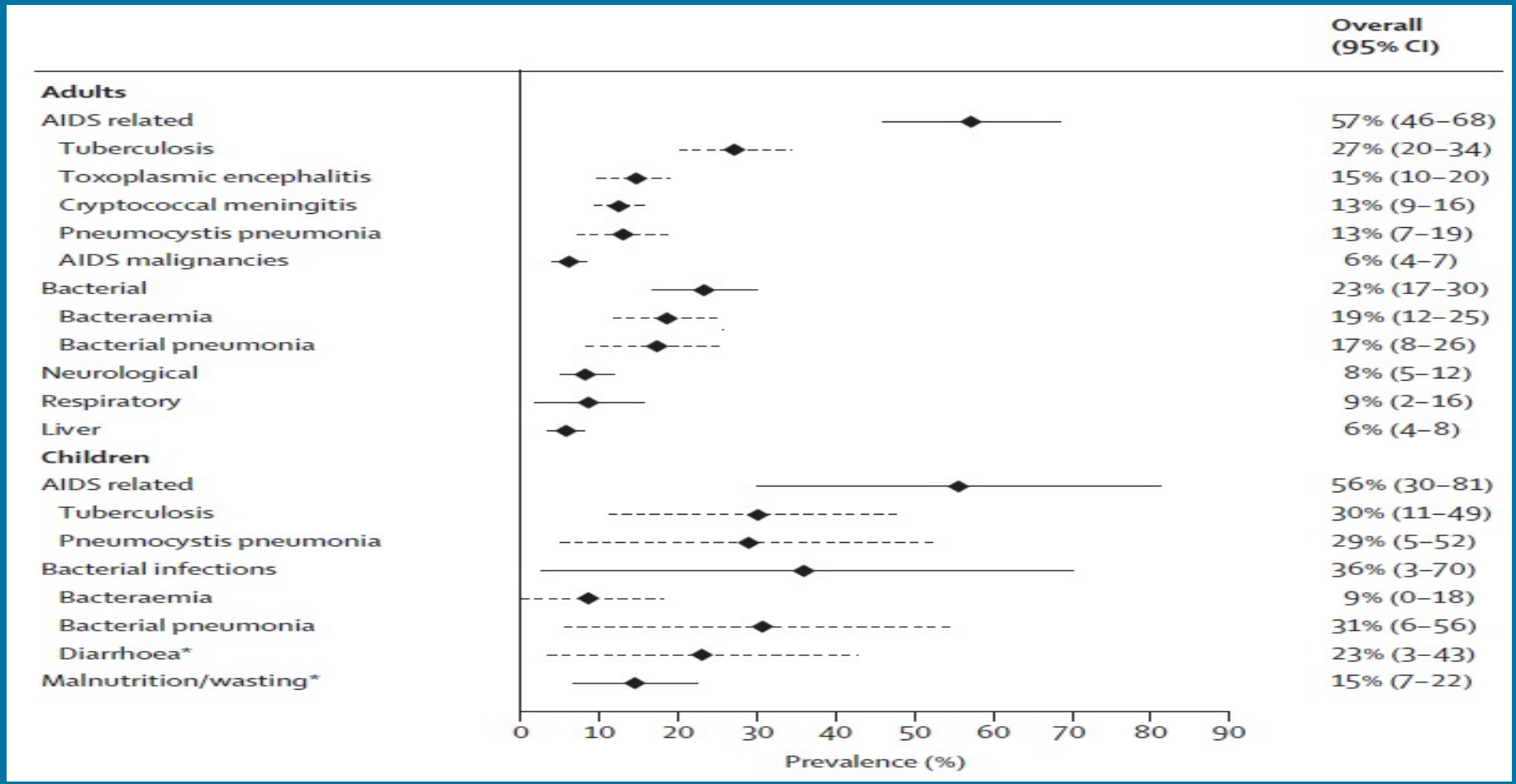
Progress on implementation of the AHD package

Dr Nathan Ford, MPH, PhD, FRCPE

Dept HIV, Viral Hepatitis and STIs

Causes of mortality

World Health Organization



Ford et al, Lancet HIV 2016

Packaged interventions for AHD

World Health Organization

Cryptococcal meningitis screening and community-based early adherence support in people with advanced HIV infection starting antiretroviral therapy in Tanzania and Zambia: an open-label, randomised controlled trial

Sayoki Mfinanga, Duncan Chanda, Sokoine L Kivuyo, Lorna Guinness, Christian Bottomley, Victoria Simms, Carol Chijoka, Ayubu Masasi, Godfather Kimaro, Bernard Ngowi, Amos Kahwa, Peter Mwaba, Thomas S Harrison, Saidi Egwaga, Shabbar Jaffar, on behalf of the REMSTART trial team*

Summary

Background Mortality in people in Africa with HIV infection starting antiretroviral therapy (ART) is high, particularly in those with advanced disease. We assessed the effect of a short period of community support to supplement clinic-based services combined with serum cryptococcal antigen screening.

Methods We did an open-label, randomised controlled trial in six urban clinics in Dar es Salaam, Tanzania, and Lusaka, Zambia. From February, 2012, we enrolled eligible individuals with HIV infection (age ≥18 years, CD4 count of <200 cells per μL, ART naive) and randomly assigned them to either the standard clinic-based care supplemented with community support or standard clinic-based care alone, stratified by country and clinic, in permuted block sizes of ten. Clinic plus community support consisted of screening for serum cryptococcal antigen combined with antifungal therapy for patients testing antigen positive, weekly home visits for the first 4 weeks on ART by lay workers to provide support, and in Tanzania alone, re-screening for tuberculosis at 6–8 weeks after ART initiation. The primary endpoint was all-cause mortality at 12 months, analysed by intention to treat. This trial is registered with the International Standard Randomised Controlled Trial Number registry, number ISCRTN 20410413.

Findings Between Feb 9, 2012, and Sept 30, 2013, 1001 patients were randomly assigned to clinic plus community support and 998 to standard care. 89 (9%) of 1001 participants in the clinic plus community support group did not receive their assigned intervention, and 11 (1%) of 998 participants in the standard care group received a home visit or a cryptococcal antigen screen rather than only standard care. At 12 months, 25 (2%) of 1001 participants in the clinic plus community support group and 24 (2%) of 998 participants in the standard care group had been lost to follow-up, and were censored at their last visit for the primary analysis. At 12 months, 134 (13%) of 1001 participants in the clinic plus community support group had died compared with 180 (18%) of 998 in the standard care group. Mortality was 28% (95% CI 10–43) lower in the clinic plus community support group than in standard care group (p=0·004).

Interpretation Screening and pre-emptive treatment for cryptococcal infection combined with a short initial period of adherence support after initiation of ART could substantially reduce mortality in HIV programmes in Africa.

Funding European and Developing Countries Clinical Trials Partnership.

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Introduction

About 10 million people in Africa are now receiving antiretroviral therapy (ART) for the treatment of HIV infection. Mortality in Africans during the first year of ART is higher than in Europeans, particularly during the first few months of treatment.[1] Additionally, in Africa, mortality[2,3] and loss to follow-up[4] are high during the pretreatment period between a patient's first presentation to clinic and ART initiation. About a third of Africans still begin ART with advanced disease,[5,6] and have a very high disease burden.

Tuberculosis and cryptococcal meningitis account for most deaths in people with HIV infection presenting at health facilities in Africa.[7–9] For tuberculosis, the median diagnostic delay is about 2 months overall[10] and diagnosis in people co-infected with HIV presenting with advanced HIV disease is particularly challenging.[11] In autopsy studies, tuberculosis has been detected in more than 50% of adults with HIV infection.[12] Cryptococcal meningitis occurs mostly in individuals with a CD4 count of less than 100 cells per μL[13] and is associated with 25–50% mortality in clinical trials and well functioning clinical settings.[3,14] The mortality associated with cryptococcal meningitis has remained high in some settings despite increased access to ART.[15,16]

The biggest challenge facing health-care delivery in Africa is the severe shortage of qualified health-care workers, particularly doctors.[17] Findings of a cluster-randomised trial[18] showed that home-based care delivered by trained lay workers was as effective as standard clinic-based care in a predominately rural setting where access to clinics was difficult.

REMSTART, Lancet 2015
REALITY NEJM 2017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Enhanced Prophylaxis plus Antiretroviral Therapy for Advanced HIV Infection in Africa

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ABSTRACT

BACKGROUND

In sub-Saharan Africa, among patients with advanced human immunodeficiency virus (HIV) infection, the rate of death from infection (including tuberculosis and cryptococcus) shortly after the initiation of antiretroviral therapy (ART) is approximately 10%.

METHODS

In this factorial open-label trial conducted in Uganda, Zimbabwe, Malawi, and Kenya, we enrolled HIV-infected adults and children 5 years of age or older who had not received previous ART and were starting ART with a CD4+ count of fewer than 100 cells per cubic millimeter. They underwent simultaneous randomization to receive enhanced antimicrobial prophylaxis or standard prophylaxis, adjunctive raltegravir or no raltegravir, and supplementary food or no supplementary food. Here, we report on the effects of enhanced antimicrobial prophylaxis, which consisted of continuous trimethoprim–sulfamethoxazole plus at least 12 weeks of isoniazid–pyridoxine (coformulated with trimethoprim–sulfamethoxazole in a single fixed-dose combination tablet), 12 weeks of fluconazole, 5 days of azithromycin, and a single dose of albendazole, as compared with standard prophylaxis (trimethoprim–sulfamethoxazole alone). The primary end point was 24-week mortality.

RESULTS

A total of 1805 patients (1733 adults and 72 children or adolescents) underwent randomization to receive either enhanced prophylaxis (906 patients) or standard prophylaxis (899 patients) and were followed for 48 weeks (loss to follow-up, 3.1%). The median baseline CD4+ count was 37 cells per cubic millimeter, but 854 patients (47.3%) were asymptomatic or mildly symptomatic. In the Kaplan–Meier analysis at 24 weeks, the rate of death with enhanced prophylaxis was lower than that with standard prophylaxis (80 patients [8.9% vs. 108 [12.2%]; hazard ratio, 0.73; 95% confidence interval [CI], 0.55 to 0.98; P=0.03); 98 patients (11.0%) and 127 (14.4%), respectively, had died by 48 weeks (hazard ratio, 0.76; 95% CI, 0.58 to 0.99; P=0.04). Patients in the enhanced-prophylaxis group had significantly lower rates of tuberculosis (P=0.02), cryptococcal infection (P=0.01), oral or esophageal candidiasis (P=0.02), death of unknown cause (P=0.03), and new hospitalization (P=0.03). However, there was no significant between-group difference in the rate of severe bacterial infection (P=0.32). There were nonsignificantly lower rates of serious adverse events and grade 4 adverse events in the enhanced-prophylaxis group (P=0.08 and P=0.09, respectively). Rates of HIV viral suppression and adherence to ART were similar in the two groups.

CONCLUSIONS

Among HIV-infected patients with advanced immunosuppression, enhanced antimicrobial prophylaxis combined with ART resulted in reduced rates of death at both 24 weeks and 48 weeks without compromising viral suppression or increasing toxic effects. (Funded by the Medical Research Council and others; REALITY Current Controlled Trials number, ISRCTN43622374.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. A. Walker at MRC Clinical Trials Unit at UCL, Aviation House, 125 Kingsway, London WC2B 6NH, United Kingdom, or at rmjlasw@ucl.ac.uk.

*A complete list of the members of the Reduction of Early Mortality in HIV-Infected Adults and Children Starting Antiretroviral Therapy (REALITY) trial team is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Prendergast, A. Walker, and Gibb contributed equally to this article.

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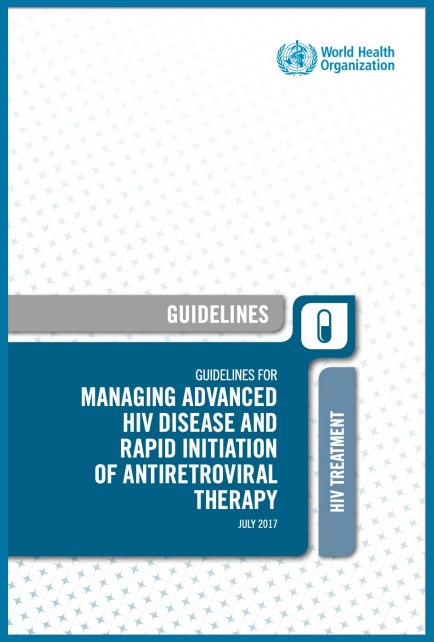
WHO Recommendation

World Health Organization



A package of interventions including screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation* and intensified adherence support interventions should be offered to everyone presenting with advanced HIV disease

Strong recommendation, moderate-quality evidence

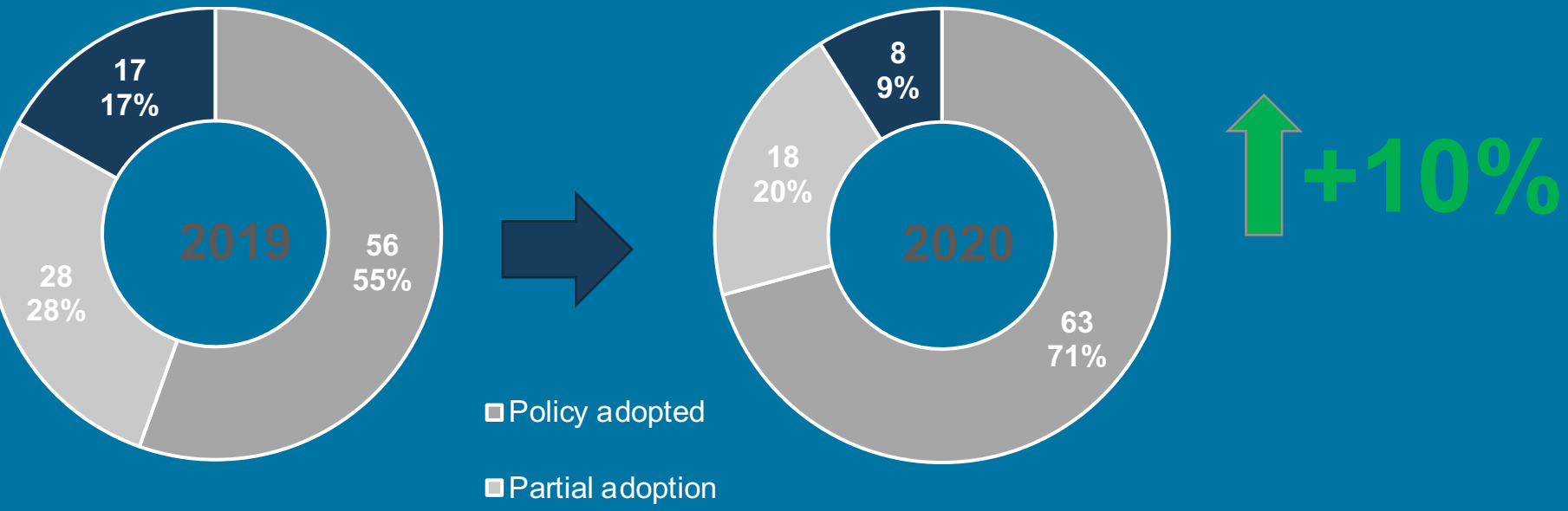
Table 1 Components of the package of care for people with advanced HIV disease

	Intervention	CD4 cell count	Adults	Adolescents	Children
Diagnosis	Sputum Xpert® MTB/RIF as the first test for TB diagnosis among symptomatic people	Any	Yes	Yes	Yes
	LF-LAM for TB diagnosis among people with symptoms and signs of TB	≤100 cells/mm³ Or at any CD4 count if seriously ill	Yes	Yes	Yes[a]
	Cryptococcal antigen screening	≤100 cells/mm³	Yes	Yes	No
Prophylaxis and pre-emptive treatment	Co-trimoxazole prophylaxis[b]	≤350 cells/mm³ or clinical stage 3 or 4 Any CD4 count in settings with high prevalence of malaria or severe bacterial infections	Yes	Yes	Yes For criteria, see Annex 1
	TB preventive treatment[b]	Any	Yes	Yes	Yes[c]
	Fluconazole pre-emptive therapy for cryptococcal antigen–positive people without evidence of meningitis	<100 cells/mm³	Yes	Yes	Not applicable (screening not advised)
ART initiation	Rapid ART initiation (as recommended in Chapter 3)	Any	Yes	Yes	Yes
	Defer initiation if clinical symptoms suggest TB or cryptococcal meningitis (see Chapter 3)	Any	Yes	Yes	Yes
Adapted adherence support	Tailored counselling to ensure optimal adherence to the advanced disease package, including home visits if feasible	<200 cells/mm³	Yes	Yes	Yes

World Health Organization

Country adopted recommendation to offer interventions for AHD : 2019-2020

World Health Organization



2019
56 countries

2020
67 countries

UNAIDS data: 116 country responses

Prioritization of people with AHD: 2017-2019

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+7%

2017
67 countries

2019
74 countries

UNAIDS data: 110 country responses

*No data available 2018/2020

Next steps

World Health Organization

AHD in Consolidated Guidelines

Review core package of care

- Severe bacterial infections

Review regional adaptations