



Going from evidence to policy and practice: 10 years of developing global HIV guidelines at WHO

Nathan Ford

Dept HIV, Viral Hepatitis and STIs

World Health Organization

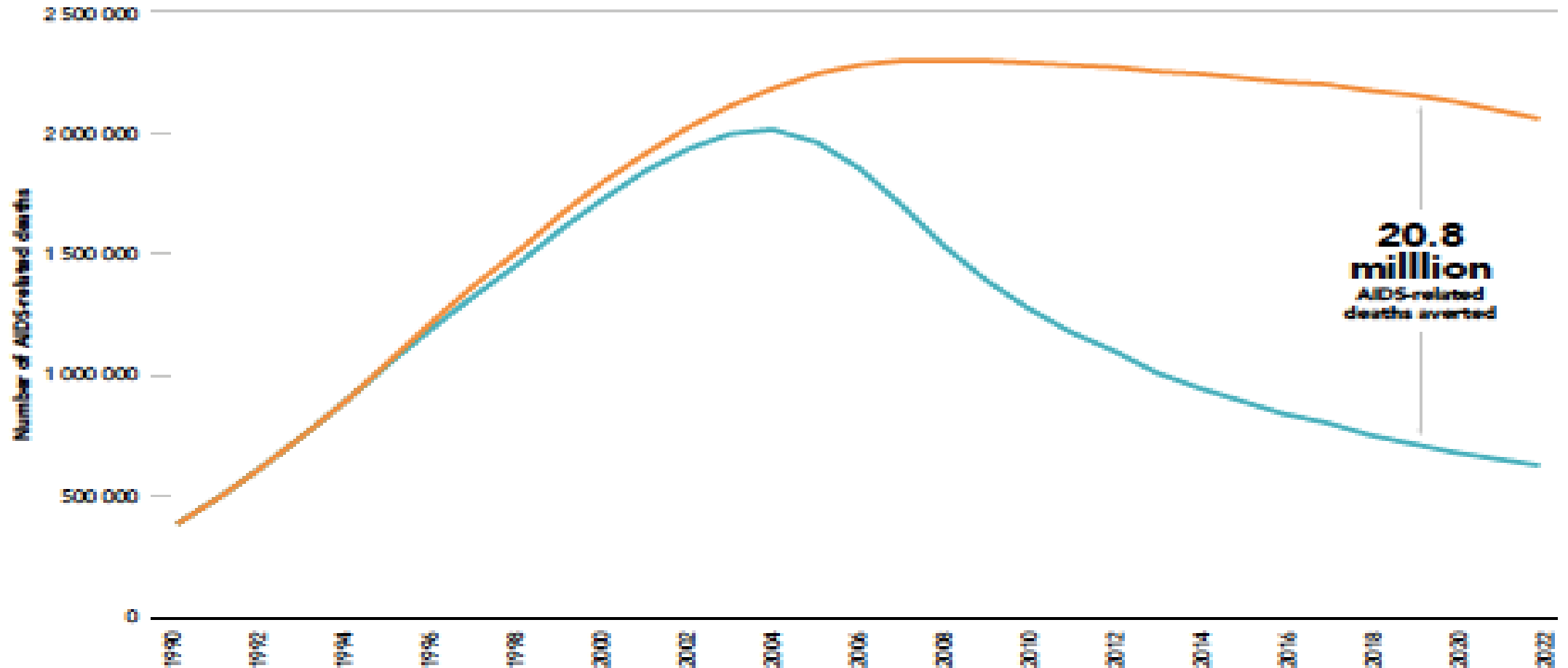
Conflict of Interest

I have no conflicts of interest

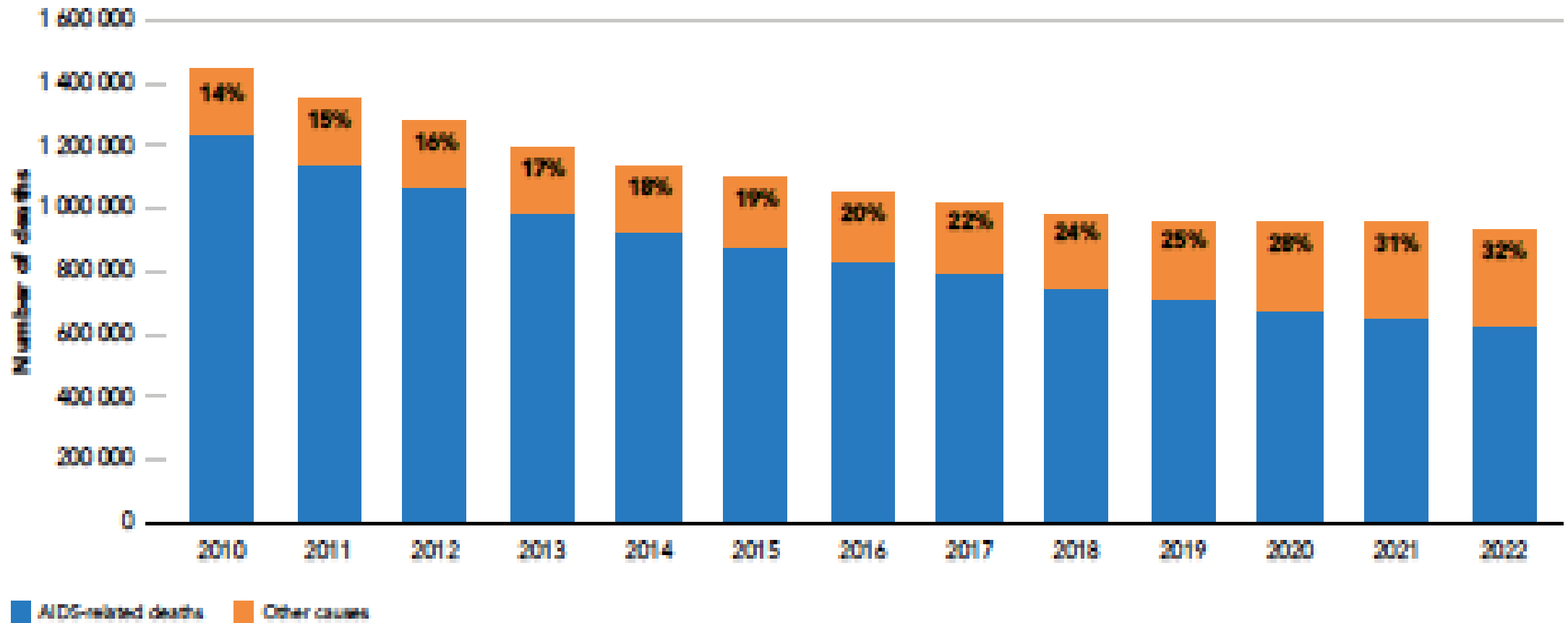


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ART has saved millions of lives



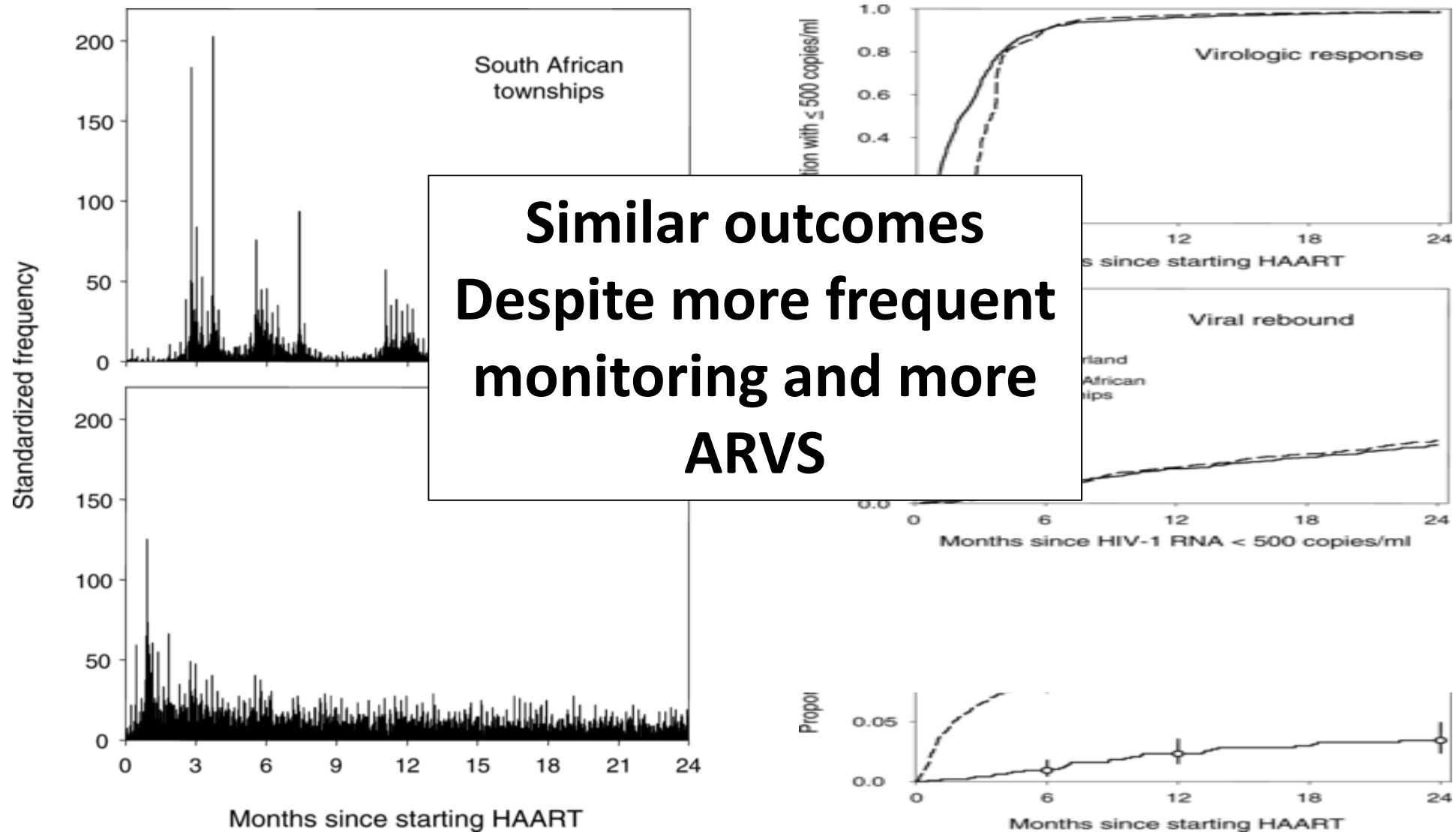
Causes of death among people living with HIV



	2006	2016
When to start ART in adults	CD4 count <200 cells per μL ; WHO clinical stage 3 or 4	As soon as possible after diagnosis
Prevention of mother-to-child transmission for pregnant women	Antepartum: zidovudine starting at 28 weeks; intrapartum: single dose nevirapine + zidovudine + lamivudine; post partum: zidovudine + lamivudine for 7 days	Immediate, lifelong ART for all pregnant women
When to start ART in children and adolescents	Age-based CD4 cell count or percentage thresholds; WHO clinical stage 3 or 4	As soon as possible after diagnosis
Starting regimen for adults	Six possible preferred regimens based on two NRTIs (zidovudine or tenofovir + lamivudine or emtricitabine) and one NNRTI (nevirapine or efavirenz)	Single preferred regimen tenofovir + lamivudine (or emtricitabine) + efavirenz
Starting regimen for children and adolescents	Six possible regimens based on two NRTIs (zidovudine or stavudine or abacavir + lamivudine) and one NNRTI (nevirapine or efavirenz)	Regimens based on age bands; <3 years: zidovudine or abacavir + lamivudine + lopinavir/ritonavir; 3–10 years: abacavir + lamivudine + efavirenz; >10 years: tenofovir + lamivudine or emtricitabine + efavirenz
Monitoring	Clinical or CD4 count monitoring (every 6 months)	Viral load (annual)
Treatment facilities	Health district	All health facilities
Treatment providers	Clinical team including doctors, clinical officers, and nurses	Doctors, nurses, or midwives

ART=antiretroviral therapy. NRTI=nucleoside reverse transcriptase inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor.

Individual vs public health approach

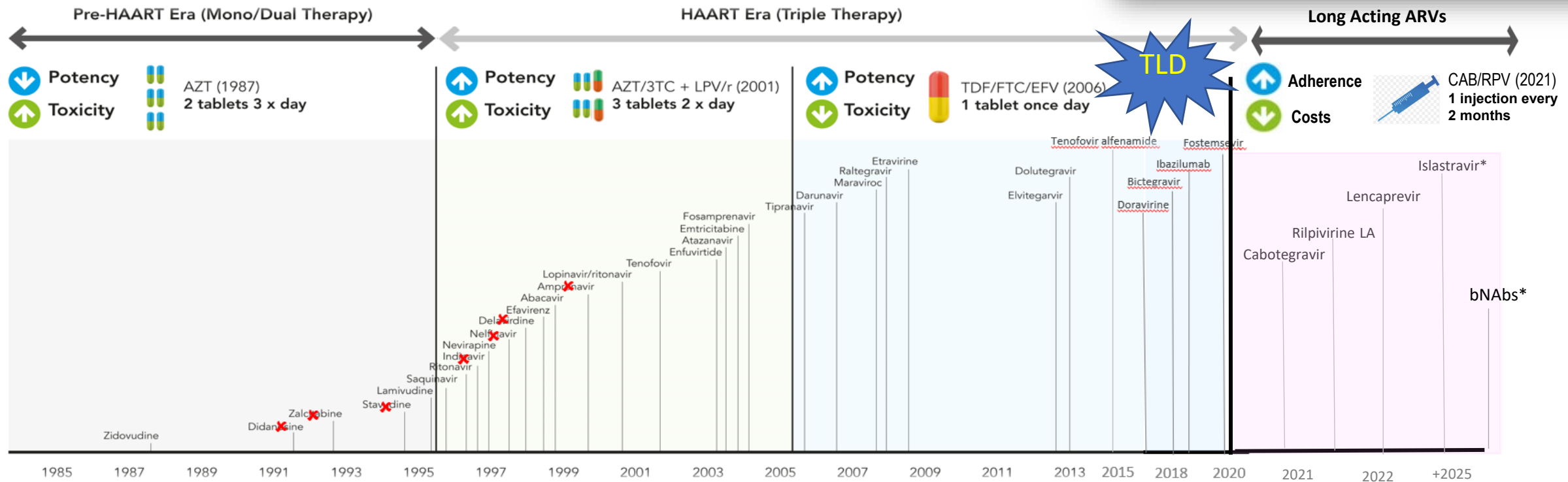


	UK	WHO
Rapid ART	2-4 weeks	7 days
Same Day start	Offer	Offer
Genotyping	Yes	No
CD4	Baseline 3-6 month if <200 12 months if 200-350 Drop if suppressed	Baseline and return to care Drop if suppressed
What to start	>9 (TDF and TAF)	1
Switch (if suppressed)	Yes	No
Nurse initiation (ART)	No	Yes
Nurse initiation (P[r]EP)	Yes	Yes

Towards smarter and better HIV treatment options



+30 medicines from 10 drug classes approved for clinical use



* expected

Evolution of HIV and treatment needs

PAST

- AIDS defining illnesses (OIs)
- Improve survival
- Reduce morbimortality
- Late diagnosis/ presentation
- HIV services (hospital/clinics)
- Start ART (progressively earlier)

PRESENT (AND FUTURE)

- Chronic comorbidities (NCDs)
- Improve QoL
- Aging
- Polypharmacy
- Pill fatigue/LFU/reengagement
- Integrated care/ Telemedicine
- PHC and Community services
- Stay on treatment (progressively longer)

Differentiated service delivery

CLIENT PERSPECTIVE

- **Why is this line so long?**
- How will I keep my job if I have to spend a day each month at this clinic?
- Why must I queue to see a nurse and then queue at the pharmacy when all I need is my ART refill?
- This place is full of sick people, but I feel healthy. Why should I keep coming?



HEALTH CARE WORKER PERSPECTIVE

- **How am I going to provide quality care to more than 100 people each day?**
- How can we support clients who are ill when we are overwhelmed with the healthy adherent clients?
- Hasn't anyone come up with a better way to deliver ART that does not compromise clinical outcomes?

WHEN

Monthly
Every 2 months
Every 3 months
Every 6 months

WHERE

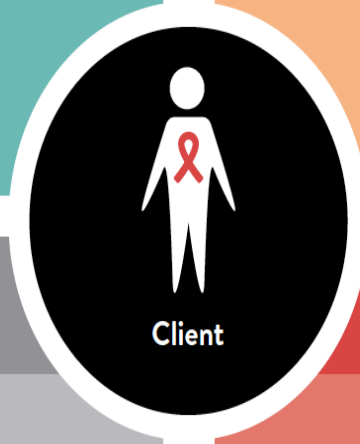
HIV clinic / hospital
Primary care clinic
Other clinic
Community
Home

WHO

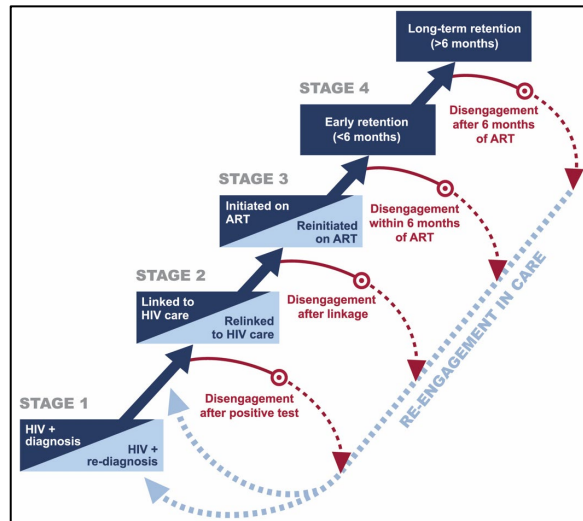
Physician
Clinical officer
Nurse
Pharmacist
Community health worker
Patient / peer / family

WHAT

ART initiation / refills
Clinical monitoring
Adherence support
Laboratory tests
OI treatment
Psychosocial support



Increasingly, ART initiators are not treatment-naive



Ehrenkranz, Plos Med 2021

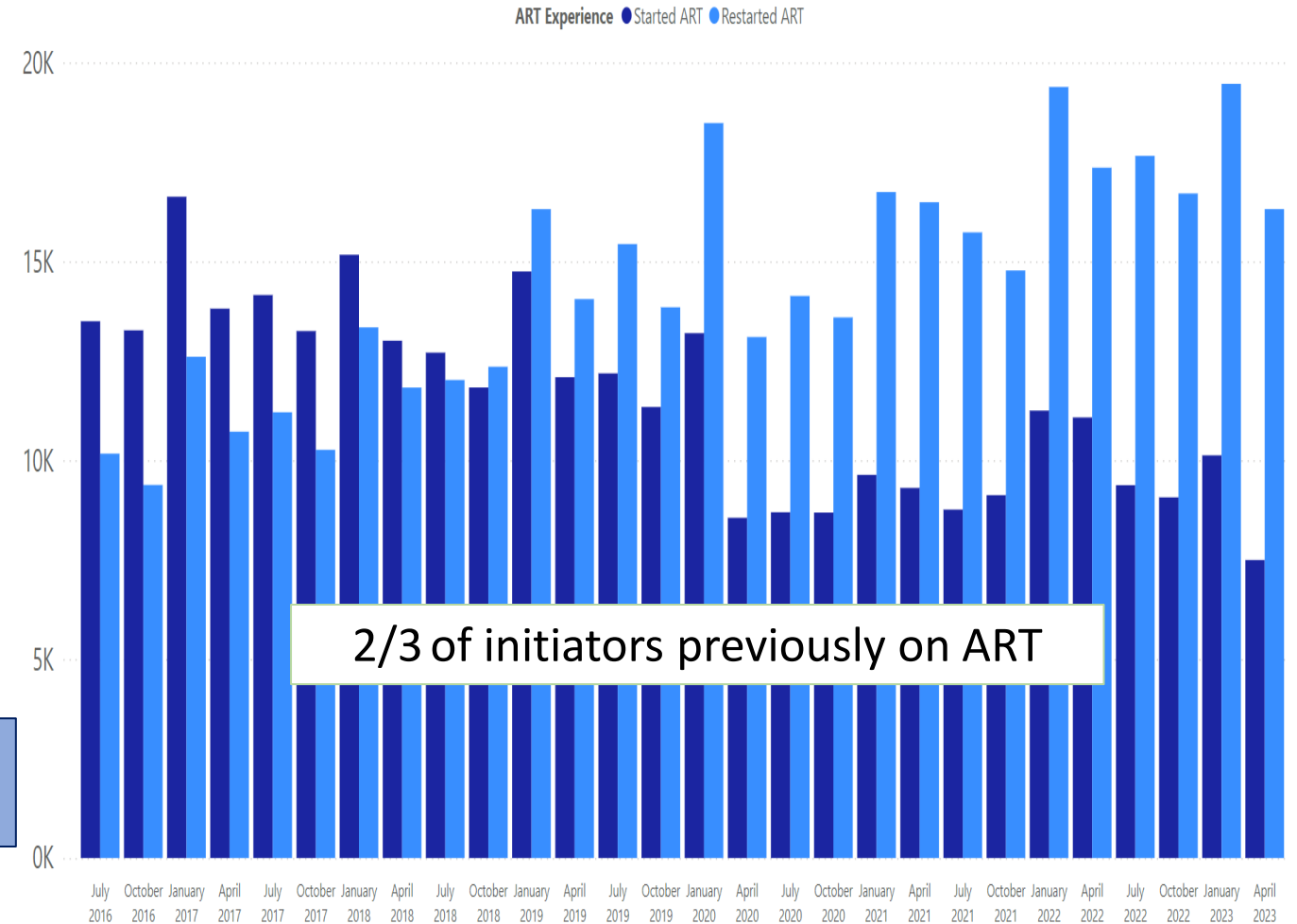
Open access Original research

BMJ Open Prior exposure to antiretroviral therapy among adult patients presenting for HIV treatment initiation or reinitiation in sub-Saharan Africa: a systematic review

20-50% are reinitiating

Mariet Benade,^{1,2} Mhairi Maskew,² Allison Juntunen,¹ David B Flynn,³ Sydney Rosen^{1,2}

Benade, BMJ Open 2023

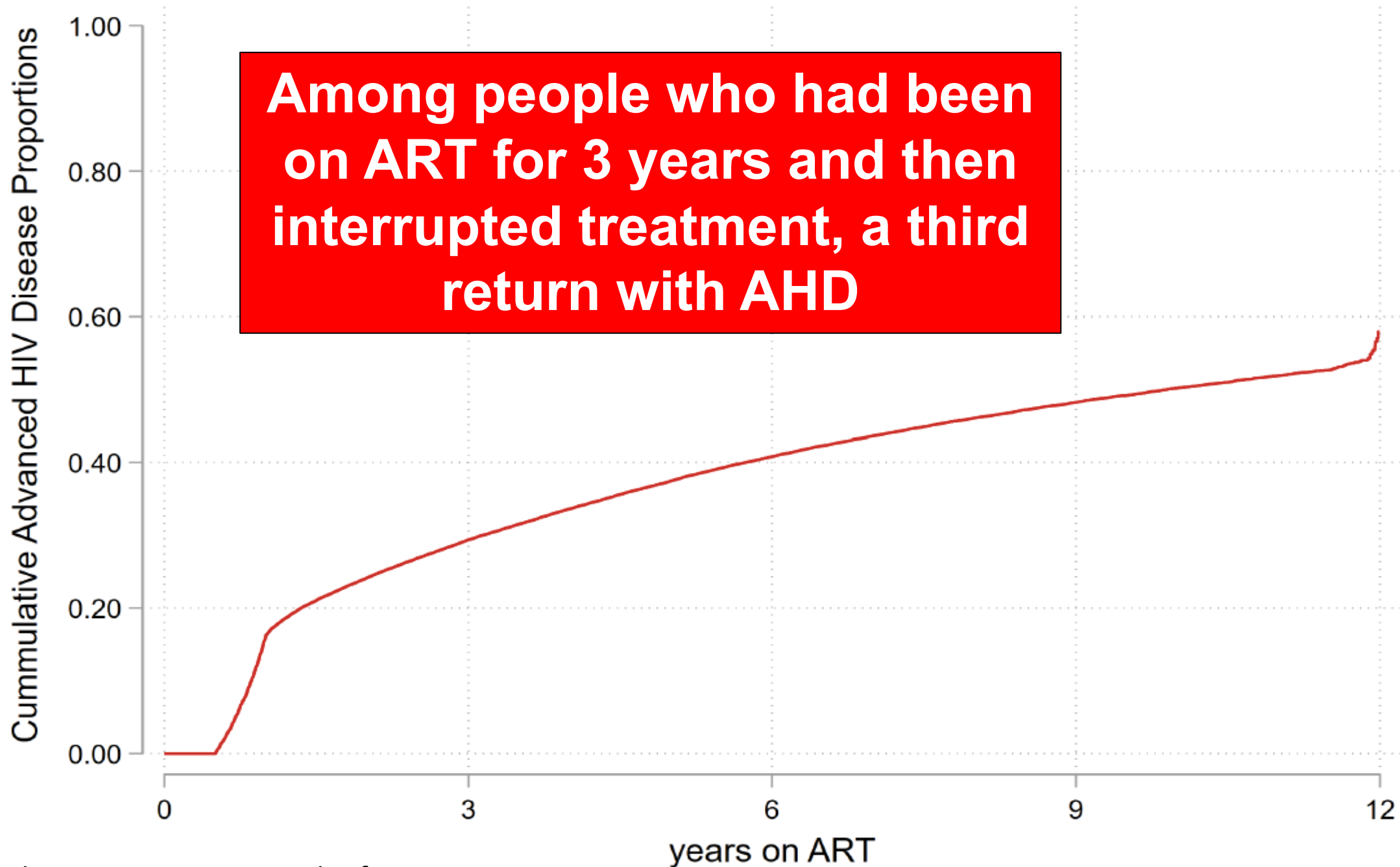


Retention & linkage to care

More people with HIV in England have dropped out of care than remain undiagnosed

Gus Cairns | 11 May 2023

As many as 20,000 of the approximately 96,000 people in England who are living with HIV may not be virally suppressed, so could potentially be able to transmit the infection to others, the British HIV Association Conference heard in Gateshead last month.



Advanced HIV Disease

Clinical Infectious Diseases
MAJOR ARTICLE

Global Trends in CD4 Cell Count at the Start of Antiretroviral Therapy: Collaborative Study of Treatment Programs

The IDeA and COHERE Cohort Collaborators*

50% <200 at start of ART

Background. Early initiation of combination antiretroviral therapy (cART), at higher CD4 cell counts, prevents disease progression and reduces sexual transmission of human immunodeficiency virus (HIV). We describe the temporal trends in CD4 cell counts at the start of cART in adults from low-income, lower-middle-income, upper-middle-income, and high-income countries (LICs, LMICs, UMICs, and HICs).

Methods. A previous analysis of cART programs and HIV cohort studies from low-income countries (LICs), lower-middle-income countries (LMICs), upper-middle-income countries (UMICs), and high-income countries (HICs) showed that median CD4 cell counts at the start of cART increased from 2000 to 2009 but remained below 200/μL in LICs and middle-income countries (MICs) and below 300/μL in HICs [4]. Similarly, a study published in *Morbidity and Mortality Weekly Report* [5] found that the percentage of patients starting cART with a CD4 cell count below 200/μL had decreased in 10 LICs and MICs but continued to be substantial in recent years, for example, 37% in Mozambique in 2014, or 34% in Haiti in 2015 [5]. A meta-analysis of African studies showed that the mean estimated CD4 cell count in 2012 was 309/μL at presentation to care and 140/μL at cART initiation [6]. Similarly, a meta-regression analysis of studies in developed countries showed only a small increase in the CD4 cell count at presentation from 1992 to 2011 [7].

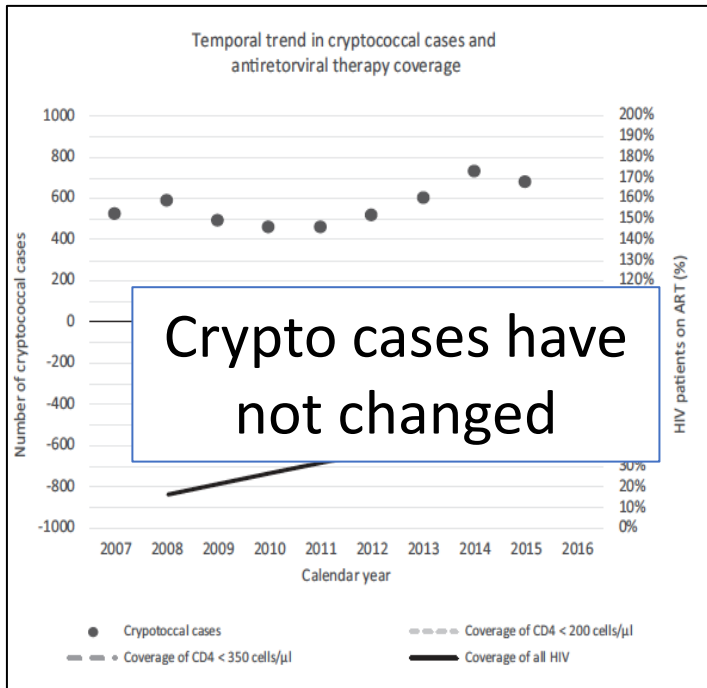
Results. For the present study, the International Epidemiology Databases to Evaluate AIDS (IDeA), a large collaboration of cART treatment programs and HIV cohort studies in the Americas, sub-Saharan Africa, and Asia-Pacific joined forces with the Collaborative of Observational HIV Epidemiological Research in Europe (COHERE) to examine global trends in CD4 cell counts at cART initiation.

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*See Acknowledgments for full list of contributing members.

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Crypto cases have not changed

Enhanced Prophylaxis plus Antiretroviral Therapy for HIV Infection in Sub-Saharan Africa

J. Hakim, V. Musi, S.L. Patt, M. Bwa, G. Musoro, S. Kabali, C. Kityo, P. M...

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

Background. In people in Africa, the rate of cryptococcal meningitis (CM) is high, particularly in those with advanced disease. We assessed the effect of a novel period of community support to supplement clinic-based care on the incidence of CM among 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 to November 2014. We enrolled eligible individuals who were HIV-infected, had a CD4 count of <200 cells per μL, were taking and randomly assigned to either standard clinic-based care supplemented with community support or standard clinic-based care alone, stratified by country and clinic. In Tanzania, the rate of CM was 1.2% and 1.7% in the community support group and the standard care group, respectively. In Zambia, the rate of CM was 1.2% and 1.7% in the community support group and the standard care group, respectively. A total of 1805 patients were enrolled in the trial. The primary endpoint was the incidence of CM. The trial is registered with ClinicalTrials.gov, NCT01250001.

Findings. Between February 9, 2012, to November 11, 2014, we enrolled 1805 individuals who were HIV-infected, had a CD4 count of <200 cells per μL, were taking and randomly assigned to either standard clinic-based care supplemented with community support or standard clinic-based care alone, stratified by country and clinic. In Tanzania, the rate of CM was 1.2% and 1.7% in the community support group and the standard care group, respectively. In Zambia, the rate of CM was 1.2% and 1.7% in the community support group and the standard care group, respectively. A total of 1805 patients were enrolled in the trial. The primary endpoint was the incidence of CM. The trial is registered with ClinicalTrials.gov, NCT01250001.

Conclusion. 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.

Keywords: adherence, antiretroviral therapy, cryptococcal meningitis, HIV, Tanzania, Zambia.

Introduction. A focus to initiate people in Africa on new, more-effective antiretroviral therapy (ART) for the treatment of HIV infection, especially in Africa during the first year of ART, is higher than in developed countries, particularly during the first 6 months of treatment. Additionally, in Africa, mortality and loss to follow-up are high during the pre-treatment period because a patient's first presentation to clinic for ART initiation. A focus to start or African adults begin ART with advanced disease and to start early high-dose cotrimoxazole and cryptococcal meningitis screens or even drugs in people with HIV infection presenting at their clinics in Africa for sub-Saharan Africa, the median diagnostic delay in those a month or more and diagnostic delay in people not initiated with ART presenting with advanced HIV disease is particularly challenging. In many studies, interventions have been directed to those with early or advanced HIV infection. Cryptococcal meningitis screen among individuals with a CD4 count of less than 200 cells per μL and is associated with 20–30% mortality in clinical trials and well-matching clinical settings. The mortality associated with cryptococcal meningitis has remained high in some settings despite increased access to ART.

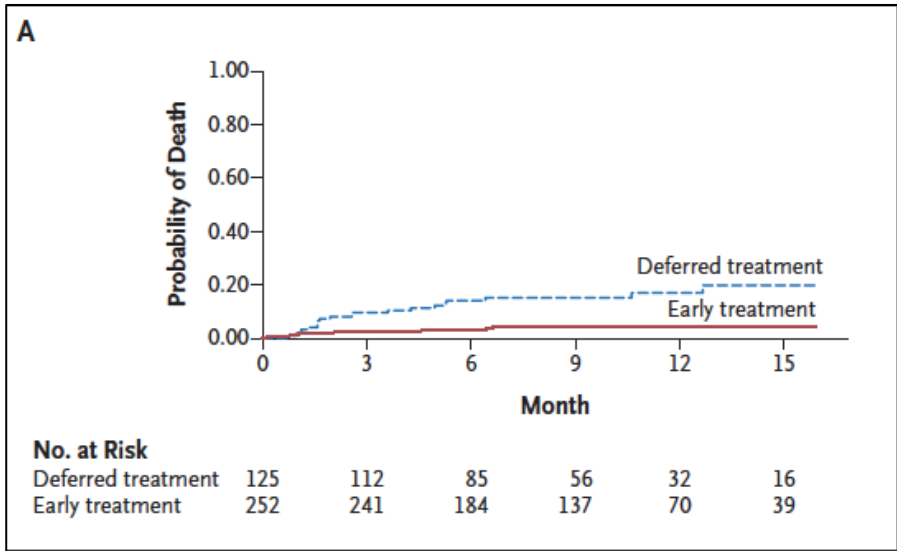
The biggest challenge being health-care delivery in Africa is the uneven coverage or quality of health-care services, particularly diagnostic testing or a cluster-randomised trial showed the home-based care delivered by trained lay workers was as effective as standard clinic-based care in a predominantly rural setting. Home-based care in clinics was effective.

A public health approach to AHD

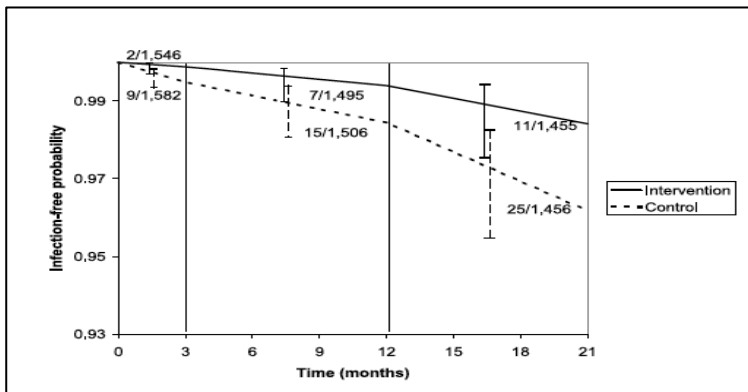
How evidence informs policy

Guideline development at WHO

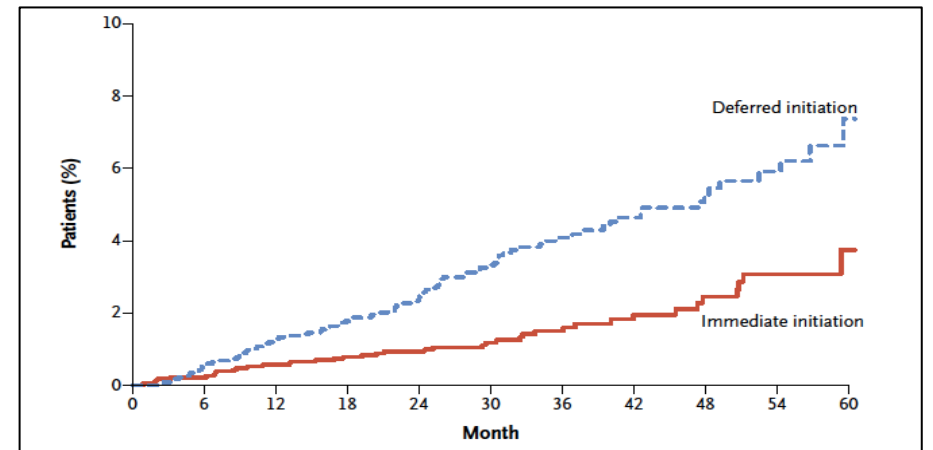
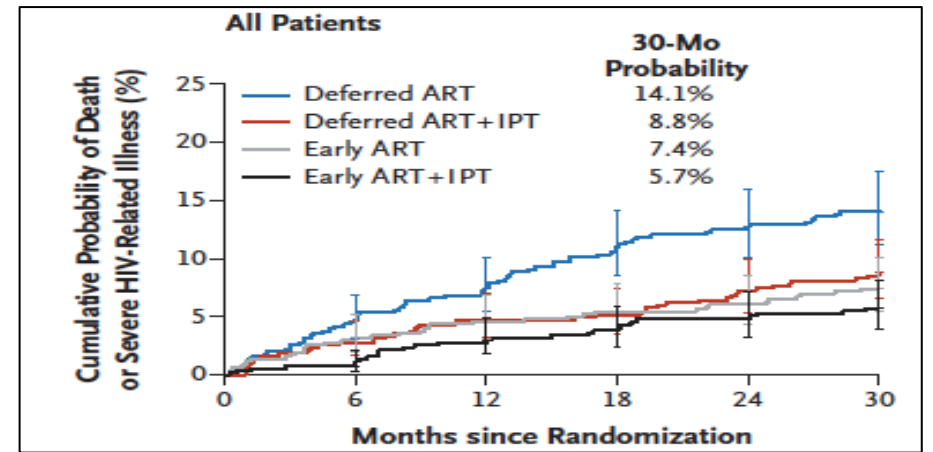
Trials can rapidly change policy and practice



Violari, NEJM 2010

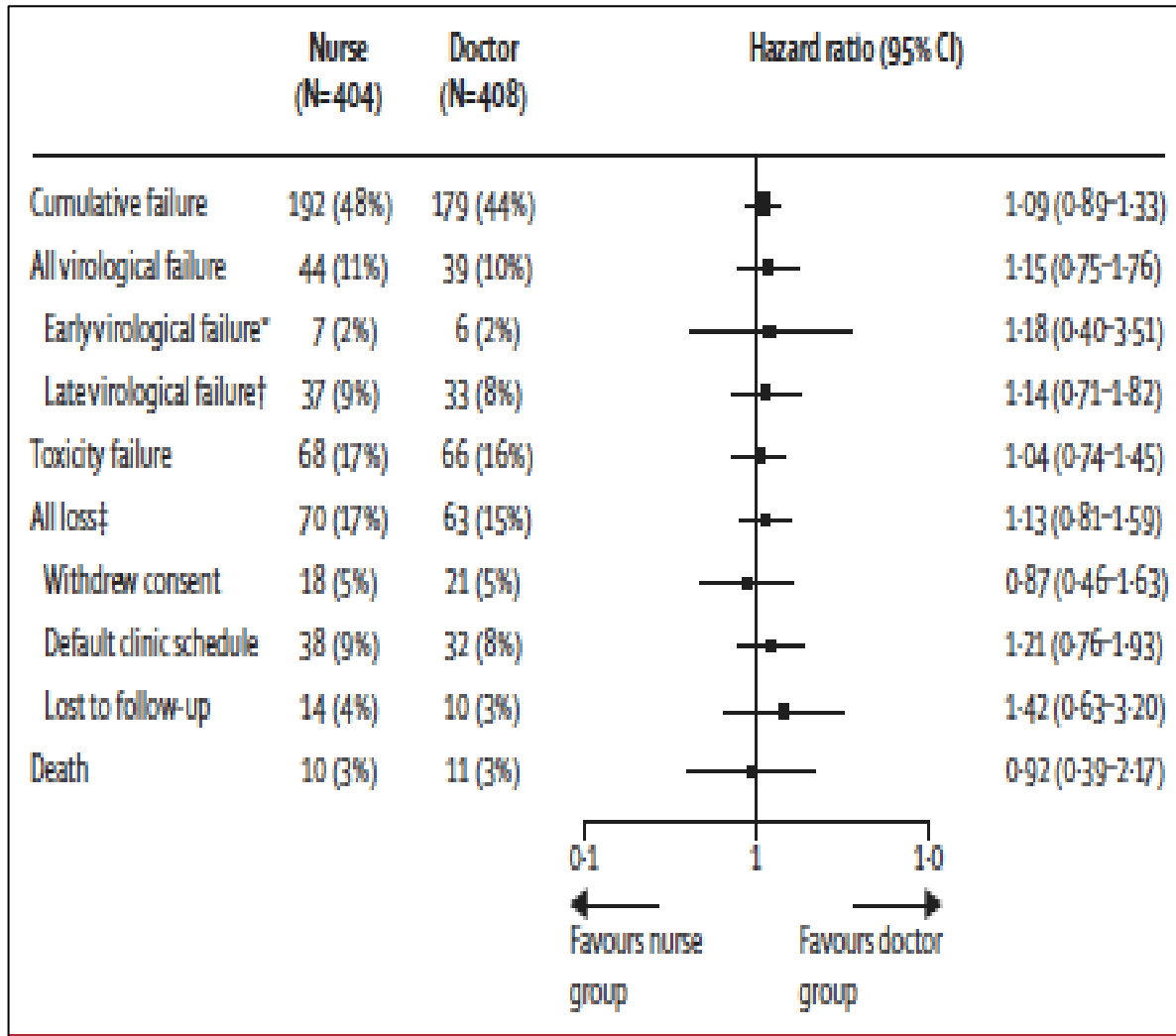


Auvert, Plos Med 2005



TEMPRANO, START 2015

Policy can change before trials



Sanne, Lancet 2010

Prevention of mother-to-child transmission of HIV and the health-related Millennium Development Goals: time for a public health approach

Erik J Schouten, Andreas Jahn, Dalitso Midiani, Simon D Makombe, Austin Mnthambala, Zengani Chirwa, Anthony D Harries, Joep J van Oosterhout, Tarek Meguid, Anne Ben-Smith, Rony Zachariah, Lutgarde Lynen, Maria Zolfo, Wim Van Damme, Charles F Gilks, Rifat Atun, Mary Shawa, Frank Chimbwandira

Schouten, Lancet 2011

Guideline development at WHO

“Evidence is generally not retrieved, appraised, synthesised, and interpreted using systematic and transparent methods.

Processes rely heavily on experts”

Use of evidence in WHO recommendations

Journal of Clinical Epidemiology 2007; 60: 1001-1007

Summary

Background: WHO regulations, dating back to 1948, emphasize the role of expert opinion in the development of recommendations. However, the organization's policies, updated in 2001, emphasize the use of systematic reviews for evidence of safety, processes that allow for the explicit incorporation of other types of information (including values) and evidence-informed deliberation and implementation strategies. We examined the use of evidence, particularly evidence of safety, in recommendations developed by WHO departments.

Methods: We interviewed department directors for their delegates at WHO headquarters in Geneva, Switzerland, and reviewed a sample of nine recommendation-containing reports and their associated background documents. Two individuals independently analysed and then reviewed and revised the reports and background documents.

Findings: Systematic reviews and concise summaries of findings are rarely used for developing recommendations. Instead, processes usually rely heavily on experts in a particular specialty. These experts' reputations or those who will use the recommendations or an expert in particular epidemiological areas.

Interpretation: Progress in the development, adaptation, dissemination, and implementation of recommendations for member states will need increasingly the resources necessary for WHO to undertake these processes in a transparent and accountable way, and close attention to the current and emerging evidence literature related to these processes.

Introduction

Every year, WHO develops a large number of recommendations aimed at many different target audiences, including the general public, health-care professionals, managers working in health facilities (eg, hospitals) or regions (eg, national and public policy-makers in member states). These recommendations address a wide range of clinical, public health, and health policy topics related to achieving health goals. WHO's regulations emphasize the role of expert opinion in the development of recommendations. In the 50 years since these regulations were initially developed, research has highlighted the limitations of expert opinion, which can differ both across disciplines and from the opinions of those who will have to live with the consequences.¹⁻⁴ Experts have also been known to use non-systematic methods when they review research, which frequently results in recommendations that do not reflect a systematic assessment of the best available evidence.^{5,6}

Evidence of the effects of alternative policies, programmes, and services is essential for well-informed decisions. Systematic reviews have several advantages over other approaches to assessing evidence of effects.⁷⁻⁹ Firstly, systematic reviews reduce the risk of bias in selecting studies and interpreting their results. Secondly, they reduce the risk of being misled by the play of chance in identifying studies for inclusion, or the risk of focusing on a limited subset of relevant evidence. Thirdly, systematic reviews provide a critical appraisal of the available evidence and place individual studies in the context of all the relevant evidence. Finally, they allow those to critically appraise the judgements made in study selection and the collection, analysis, and interpretation of the results. However, systematic reviews are only as good as the evidence that they summarise. There might be no evidence. When there is evidence, judgements are still needed about the quality and, especially for public health and health policy topics, the applicability in different contexts.¹⁰

Evidence of effects needs to be supplemented by information about costs, the harm that could affect relative effectiveness will be evident in the field, such as the availability of resources, costs, and the extent to which they will be affected by the recommendations. Processes that allow for the explicit incorporation of these types of information, particularly values, have also been shown to be useful in the development of recommendations.^{11,12} Moving from evidence to recommendations requires judgements, particularly judgements about goals and about the balance between the desirable and undesirable consequences of choosing one option over another to achieve those goals.

Evidence-informed deliberation and implementation strategies are increasingly recognised as a core part of the business of developing recommendations. These changes with developing clinical practice guidelines can draw on a systematic review or randomised controlled trials of guideline development and implementation strategies to inform their effects.^{13,14} Although there are no easy solutions and few strategies have been assessed in low-income and middle-income countries, such efforts clearly can have an effect.¹⁵ Those charged with developing recommendations targeted at managers or public policy-makers, on the other hand, have to deliberate the attributes of the interventions being systematic reviews of observational studies and begin

Downloaded from <http://www.elsevier.com/locate/jclinepi>

Journal of Clinical Epidemiology, Vol 60, No 10 (October), pp 1001-1007, 2007

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doi:10.1016/j.jclinepi.2007.05.007

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WHO

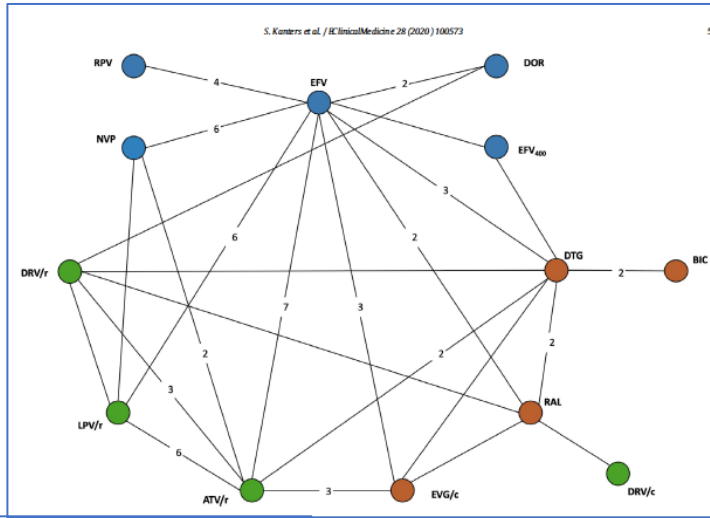
Handbook for Guideline Development

2nd edition

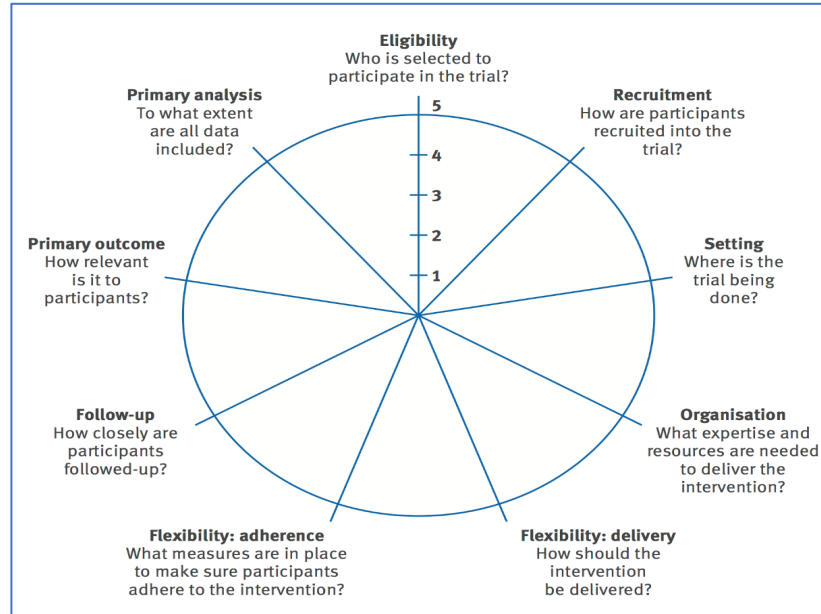


Evidence to decisions	
Safety and efficacy	RCTs, observational studies
Feasibility	Qualitative research; surveys
Acceptability	Qualitative research; surveys
Cost	Economic data; analyses
Values and preferences: provider & recipient	Qualitative research; surveys
Ethics, equity and Human rights	Qualitative research; Key considerations

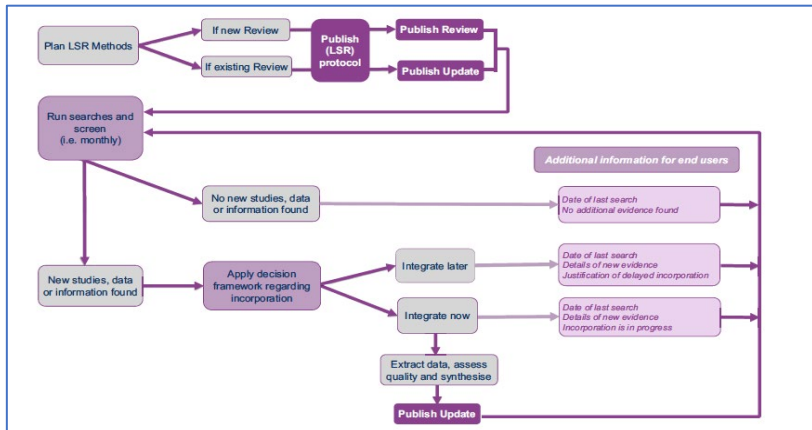
Future directions



Kanters, EClinMed 2020



Loudon The PRECIS-2 tool: designing trials that are fit for purpose. BMJ 2015



Elliott J Clin Epi 2017

Visual summary of recommendation

Population
This recommendation applies only to people with these characteristics:
Patients with confirmed covid-19

Disease severity

Non-severe	Severe	Critical
Absence of signs of severe or critical disease	SpO ₂ < 90% on room air	Requires life sustaining treatment
	Respiratory rate > 30 in adults	Acute respiratory distress syndrome
	Raised respiratory rate in children	Sepsis
	Signs of severe respiratory distress	Septic shock

Interventions

Remdesivir	Recommendation against (weak)	
Corticosteroids	Recommendation against (weak)	Recommendation in favour (strong)

Rochweg BMJ 2020

How global is global health?

Nurse versus doctor management of HIV-infected patients receiving antiretroviral therapy (CIPRA-SA): a randomised non-inferiority trial

Ian Sanne, Catherine Orrell, Matthew P Fox, Francesca Conradie, Prudence Iwe, Jennifer Zeinecker, Marnie Cornell, Christie Hetberg, Charlotte Ingram, Ravindra Panjchi, Mohammed Rasoos, René Gontin, Wendy Stevens, Heidi de Truster, Marjolje Dehlinger, Charles van der James Midnyre, Robin Wood, for the CIPRA-SA Study Team*

Summary

Background Expanded access to combination antiretroviral therapy (ART) in resource-poor settings is dependant on task shifting from doctors to other health care providers. We compared outcomes of nurse versus doctor management of ART care for HIV-infected patients.

Methods This randomised non-inferiority trial was undertaken at two South African primary-care clinics. HIV-positive individuals with a CD4 cell count of less than 350 cells per μL or WHO stage 3 or 4 disease were randomly assigned to nurse-monitored or doctor-monitored ART care. Patients were randomly assigned by stratified permuted randomisation, and neither the patients nor those analysing the data were masked to assignment. The primary objective was a composite endpoint of treatment-limiting events, incorporating mortality, viral failure, treatment-limiting toxic effects, and adherence to visit schedule. Analysis was by intention to treat. Non-inferiority of the nurse versus doctor group for cumulative treatment failure was prespecified as an upper 95% CI for the hazard ratio was less than 1.40. This study is registered with ClinicalTrials.gov, number NCT0255840.

Findings 408 patients were assigned to doctor-monitored ART care and 404 to nurse-monitored ART care. 371 (46%) patients reached an endpoint of treatment failure: 192 (48%) in the nurse and 179 (44%) in the doctor group. The hazard ratio for composite failure was 1.09 (95% CI 0.89–1.33), which was within the limits for non-inferiority. After a median follow-up of 120 weeks (IQR 60–144), deaths (ten vs 11), virological failures (44 vs 39), toxicity failures (68 vs 66), and programme losses (70 vs 63) were similar in nurse and doctor groups, respectively.

Interpretation Nurse-monitored ART is non-inferior to doctor-monitored therapy. Findings from this study support task shifting to appropriately trained nurses for monitoring of ART.

Funding National Institutes of Health; United States Agency for International Development; National Institute of Allergy and Infectious Diseases.

Introduction

Combination drug therapy has had a remarkable effect on the reduction of AIDS-related morbidity and mortality.¹ In industrialised countries, antiretroviral management is administered by specialist physicians who prescribe from the full range of available antiretroviral drugs, supported by frequent laboratory monitoring including resistance testing.² Findings from several studies in industrialised settings have shown that outpatients have better outcomes when cared for by a physician with HIV expertise than do those without such a physician, including quality of care and survival,^{3,4} which could be an indicator of the complexities of HIV infection and its management.⁵ By contrast with the small epidemic in resource-rich countries, there are 22.4 million people living with HIV in sub-Saharan Africa,⁶ with an estimated 3.8 million in urgent need of treatment.⁷ Globally, there is a shortage of 4.3 million health workers (doctors, midwives, nurses, and support workers).⁸ In South Africa there are only 17.4 medical

practitioners per 100 000 people, who are concentrated in urban areas.^{9,10} By contrast with the individualised approach to care in developed countries, WHO has proposed a health approach to antiretroviral therapy (ART) to scaling up of access to treatment for large numbers of HIV-positive adults and children in developing countries. An approach using standardised simplified treatment protocols and decentralised service delivery was developed to enable lower level health-care workers to deliver ART. Models of care have investigated task shifting to community health workers and a combination of nurses and community health workers;¹¹ however, nurse-led models of antiretroviral delivery have been one of the most widely implemented models of HIV care in poor-resourced African settings. Findings from a trial have shown that work-site training of hypertension by specially trained nurses significantly improved blood pressure control and adherence.¹² So far no randomised prospective study has been published to show the effectiveness of

Clinical Infectious Diseases

VIEWPOINTS



How Applicable Is the Single-Dose AMBITION Regimen for Human Immunodeficiency Virus-Associated Cryptococcal Meningitis to High-Income Settings

Thomas S. Harrison,^{1,2,3} David S. Lawrence,^{4,5} Henry C. Mwenda,^{6,7,8} David R. Boulware,^{9,10} Misa C. Hoeselinger,^{11,12} Olivier Craemoelje,^{13,14} Mosepolo Mosepolo,^{15,17} and Joseph N. Jarvis^{16,18}

¹Institute of Infection and Immunity, St George's University London, United Kingdom; ²Clinical Academic Group in Infection and Immunity, St George's University London, United Kingdom; ³Medical Research Council Centre for Molecular Microbiology, University of Cambridge, United Kingdom; ⁴Department of Clinical Research, The Ohio State University, Columbus, Ohio, USA; ⁵Department of Infectious Diseases, University of Liverpool, United Kingdom; ⁶Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana; ⁷Clinical School of Tropical Medicine, Liverpool, United Kingdom; ⁸Malawi Liverpool Wellcome Clinical Research Programme, Blantyre, Malawi; ⁹Department of Medicine, The Ohio State University, Columbus, Ohio, USA; ¹⁰Division of Infectious Diseases and Mycology, University of Minnesota, Minneapolis, Minnesota, USA; ¹¹Langone Medical Center, University of North Carolina Project, University of North Carolina, Chapel Hill, North Carolina, USA; ¹²Division of Infectious Diseases, University of North Carolina, Chapel Hill, North Carolina, USA; ¹³Unit of Infectious Diseases, Hôpital Pasteur, National Center for Scientific Research, Molecular Mycology Unit and National Reference Center for Invasive Fungal Infections, Paris, France; ¹⁴Unit of Infectious Diseases, Hôpital Pasteur, National Center for Scientific Research, Molecular Mycology Unit and National Reference Center for Invasive Fungal Infections, Paris, France; ¹⁵Unit of Infectious Diseases, Hôpital Pasteur, National Center for Scientific Research, Molecular Mycology Unit and National Reference Center for Invasive Fungal Infections, Paris, France; ¹⁶Department of Medicine, University of Cape Town, Cape Town, South Africa; and ¹⁷Department of Internal Medicine, University of Botswana, Gaborone, Botswana

The Ambisome Therapy Induction Optimization (AMBITION-cm) trial, conducted in eastern and southern Africa, showed that a single, high dose (10 mg/kg) of liposomal amphotericin B, given with an oral backbone of fluconazole or rifampicin, was non-inferior to the World Health Organization (WHO)-recommended regimen of 7 days of amphotericin B followed by fluconazole for treatment of human immunodeficiency virus (HIV)-associated cryptococcal meningitis and has been included in WHO treatment guidelines. We believe that the trial also has important implications for the treatment of cryptococcal meningitis in high-income settings. We advance the arguments, supported by evidence where available, that the AMBITION-cm trial regimen is likely to be as fungicidal as the currently recommended 14-day liposomal amphotericin B treatment, better tolerated with fewer adverse effects, and confer significant economic and practical benefits and should be included as a treatment option in guidance for HIV-associated cryptococcal treatment in high-income settings.

Keywords: cryptococcal meningitis; HIV; amphotericin B; fluconazole; rifampicin.

Human immunodeficiency virus-associated cryptococcal meningitis remains a significant driver of AIDS-related mortality, causing about 15% of all AIDS-related deaths. The greatest burden of disease is found in sub-Saharan Africa [1], primarily due to the persistent burden of advanced HIV disease despite widespread access to antiretroviral therapy [2]. Given the distribution of global disease burden, the vast majority of recent clinical research that guides cryptococcal management in people with HIV has been generated in low- and middle-income countries (LMICs) [3]. Although the disease burden has lessened in high-income countries, HIV-related cryptococcosis still occurs and mortality is still substantial [4], with an estimated 7400 cases and 2000 deaths

annually across Europe and North America [5]. We present an overview of the findings of the Therapy Induction Optimization (AMBITION) trial, which assessed the applicability to high-income settings of the AMBITION regimen. High-income countries have historically been overlooked in the development of WHO guidelines for high-income countries. It is important to consider when control regimens differ from the standard of care in high-income countries and when the ability to monitor and manage treatment-related complications varies, such as with the use of intravenous liposomal amphotericin B. Inappropriate use of intravenous liposomal amphotericin B in high-income countries is common. Nevertheless, we argue that the AMBITION trial data for novel treatment approaches from high-income countries, controlled trials provide critical insight into the efficacy and safety of treatment that are not available and should therefore be considered in high-income countries. We cover only HIV-associated cryptococcal meningitis; other risk groups requires specific studies.

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MAJOR ARTICLE



Revisiting the Evidence Base for Modern-Day Practice of the Treatment of Toxoplasmic Encephalitis: A Systematic Review and Meta-Analysis

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Background. Toxoplasmic encephalitis (TE) is an opportunistic infection of people with human immunodeficiency virus (HIV) or other causes of immunosuppression. Guideline-recommended treatments for TE are pyrimethamine and sulfadiazine (P-S) or pyrimethamine and clindamycin (P-C); however, a substantial price increase has limited access to pyrimethamine. Consequently, some centers have transitioned to trimethoprim-sulfamethoxazole (TMP-SMX), an inexpensive alternative treatment. We aimed to review the evidence on the efficacy and safety of pyrimethamine-containing therapies vs TMP-SMX.

Methods. We searched for and included randomized controlled trials (RCTs) and observational studies of TE treatments, regardless of HIV status. Data for each therapy were pooled by meta-analysis to assess the proportions of patients who experienced clinical and radiologic responses to treatment, all-cause mortality, and discontinuation due to toxicity. Sensitivity analyses limited to RCTs directly compared therapies.

Results. We identified 6 RCTs/dose-escalation studies and 26 single-arm/observational studies. Identified studies included only persons with HIV, and most predated modern antiretroviral treatment. Pooled proportions of clinical and radiologic response and mortality were not significantly different between TMP-SMX and pyrimethamine-containing regimens ($P > .05$). Treatment discontinuation due to toxicity was significantly lower in TMP-SMX (7.3%; 95% confidence interval [CI], 4.7–11.4; $I^2 = 0.0%$) vs P-S (30.5%; 95% CI, 27.1–34.2; $I^2 = 0.0%$; $P < .01$) or P-C (13.7%; 95% CI, 9.8–18.8; $I^2 = 32.0%$; $P = .031$). These results were consistent in analyses restricted to RCT data.

Conclusions. TMP-SMX appears to be as effective and safer than pyrimethamine-containing regimens for TE. These findings support modern RCTs comparing TMP-SMX to pyrimethamine-based therapies and a revisiting of the guidelines.

Short-Course Amphotericin-Based Treatment for Cryptococcal Meningitis: A Program of Clinical Trials across Sub-Saharan Africa
A program of clinical trials across sub-Saharan Africa was initiated in 2004. The aim was to develop

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