BHIVA
British HIV Association
Autumn Conference
Friday 24th November 2023
etc.venues 155 Bishopsgate, London
BHIVA WORLD AIDS DAY
WORLD AIDS DAY

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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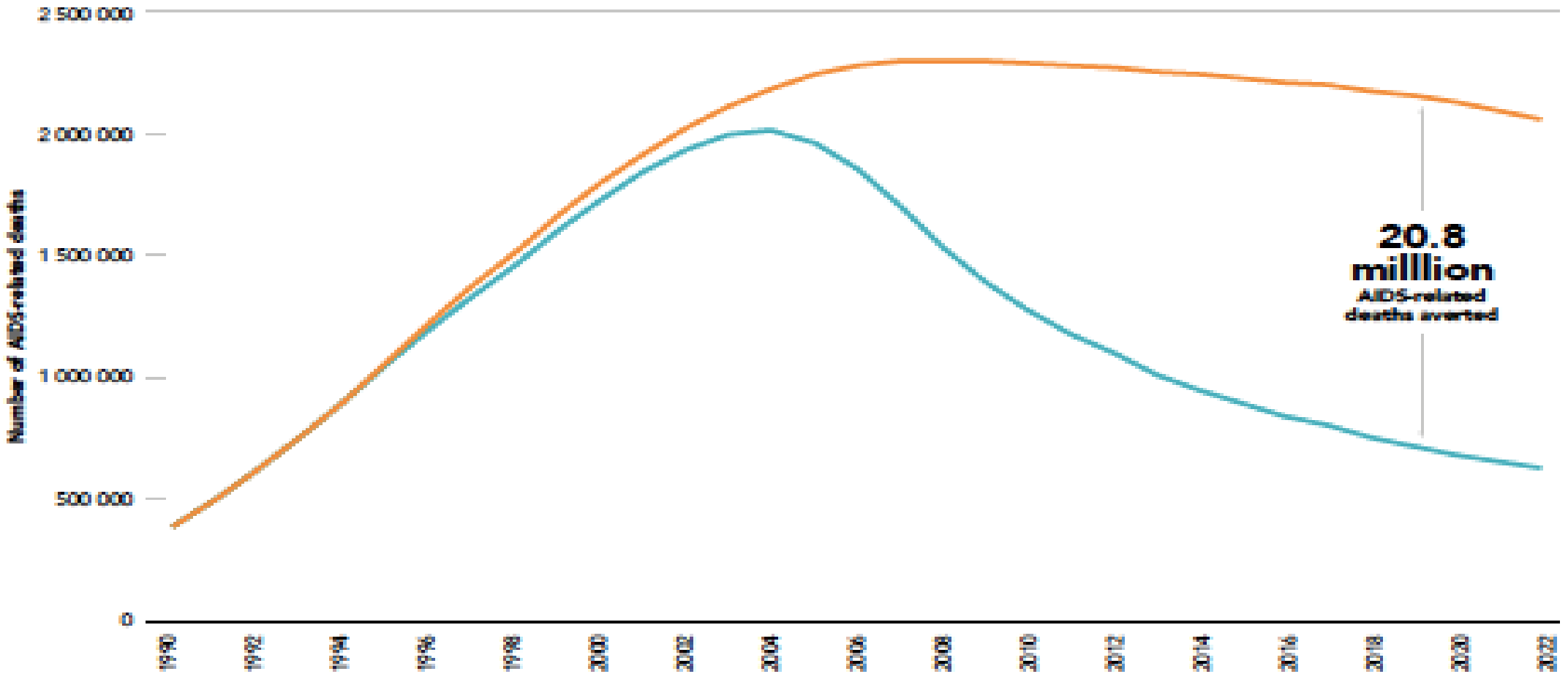
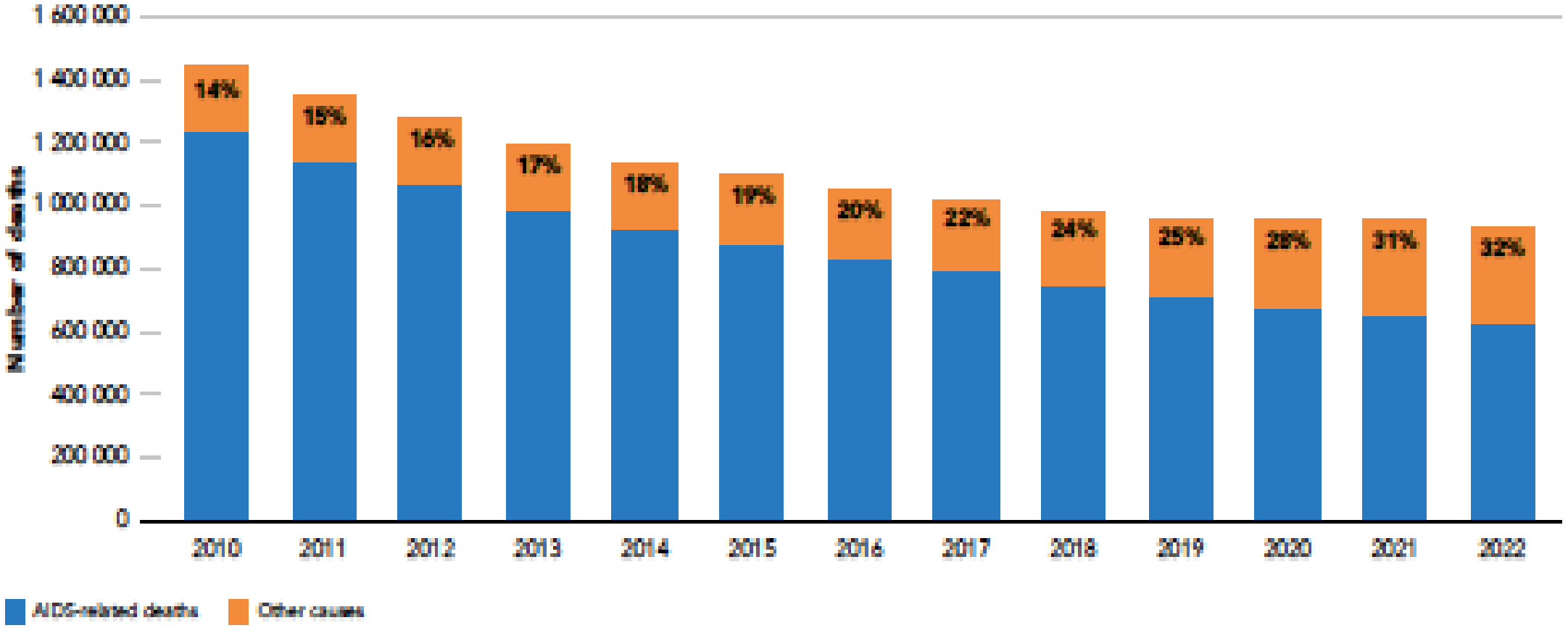
ART has saved millions of lives



UNAIDS 2023

Causes of death among people living with HIV



UNAIDS 2023

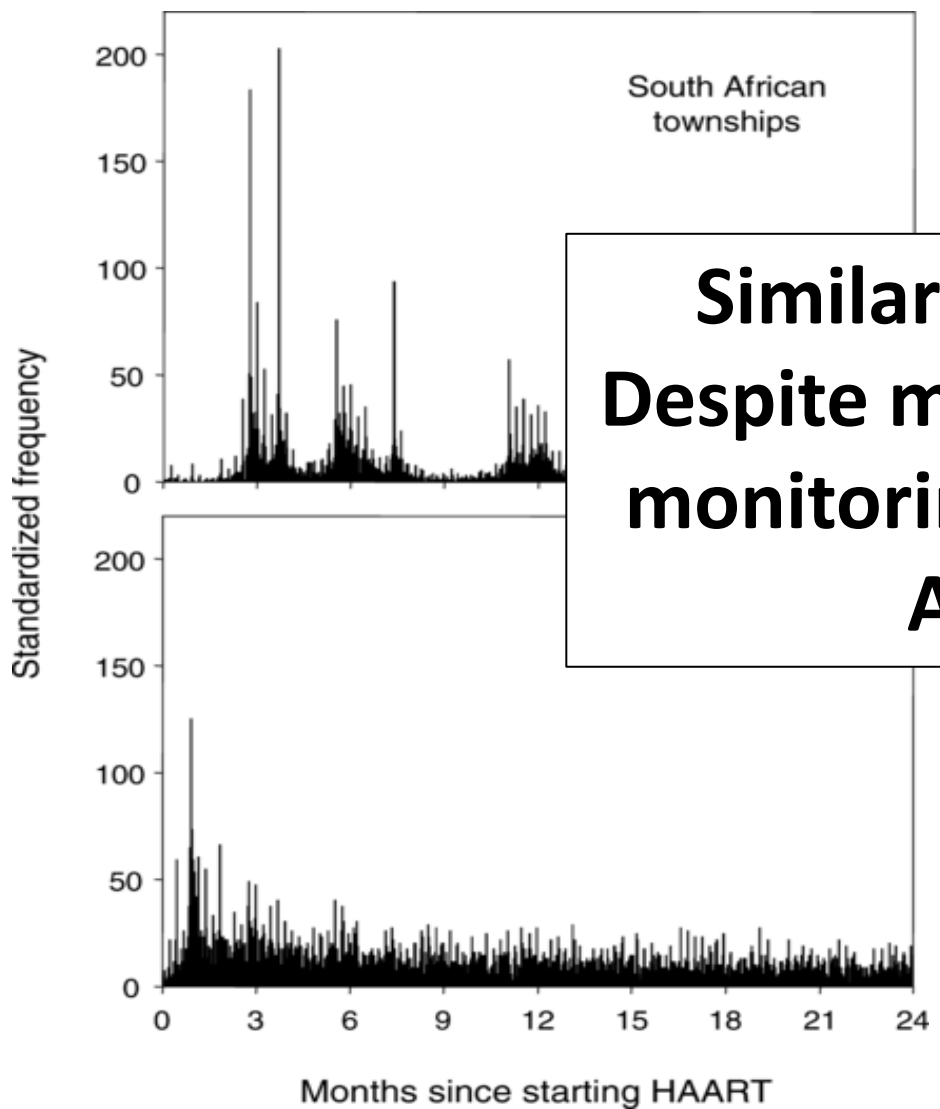
	2006	2016
When to start ART in adults	CD4 count <200 cells per μL; WHO clinical stage 3 or 4	As soon as possible after diagnosis
Prevention of mother-to-child transmission for pregnant women	Antepartum: zidovudine starting at 28 weeks; intrapartum: single dose nevirapine + zidovudine + lamivudine; post 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.

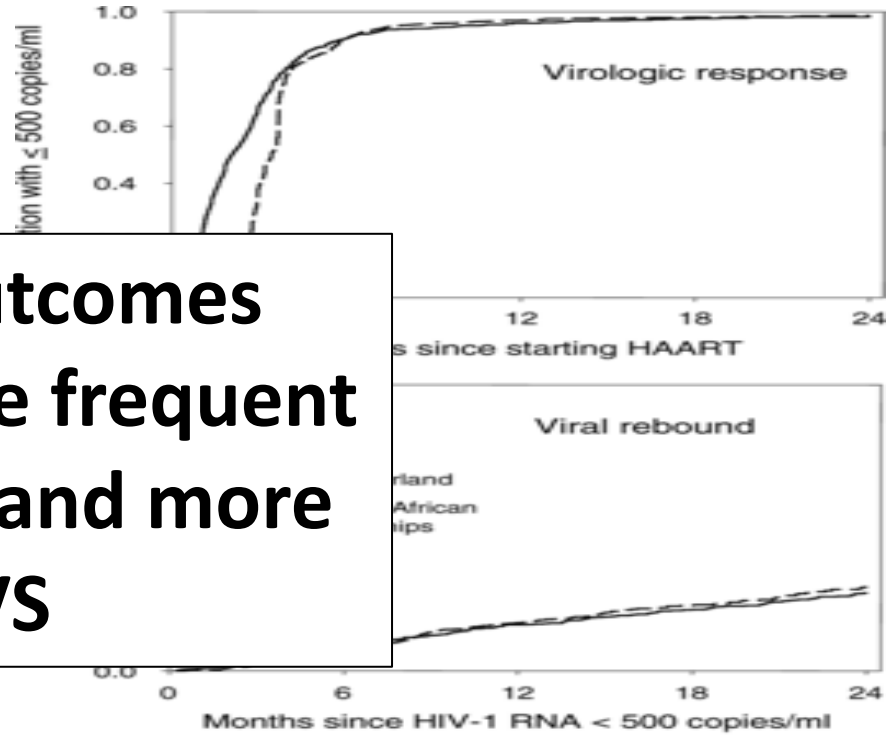
***Table 1*: Public health approach policies 2006 versus 2016**

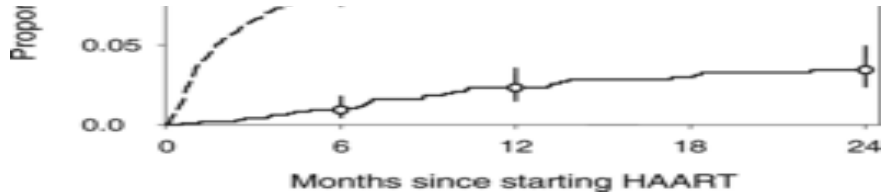
Ford et al, *Lancet Inf Dis* 2018

Individual vs public health approach



Similar outcomes Despite more frequent monitoring and more ARVS



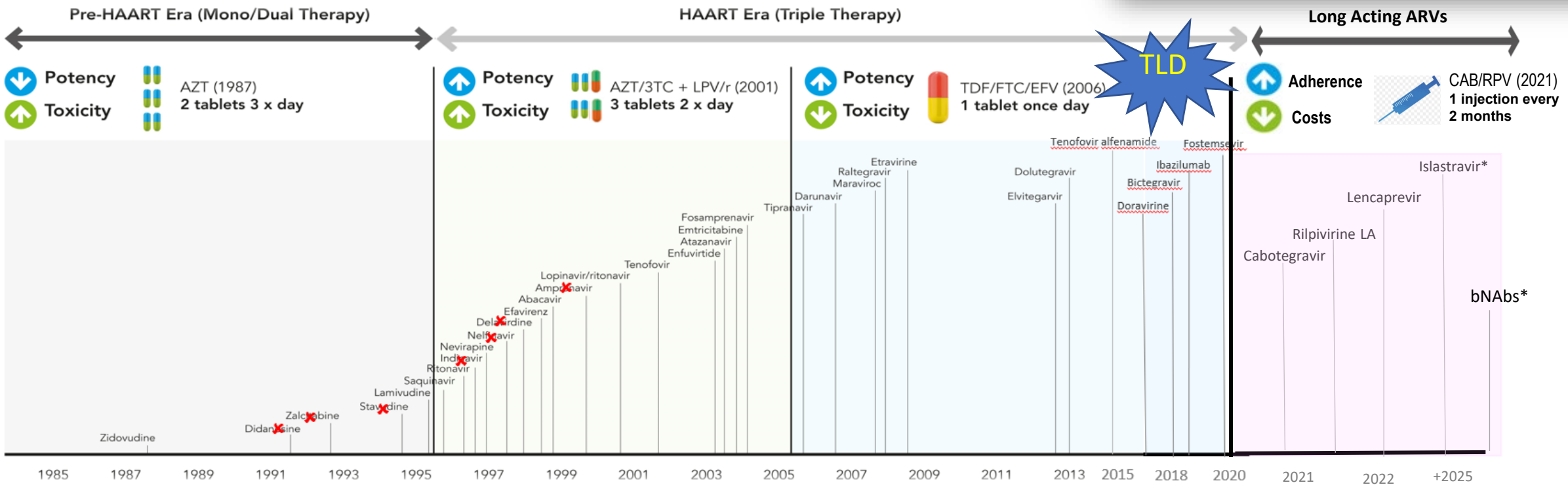


Keiser et al, Plos Medicine, 2008

	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)

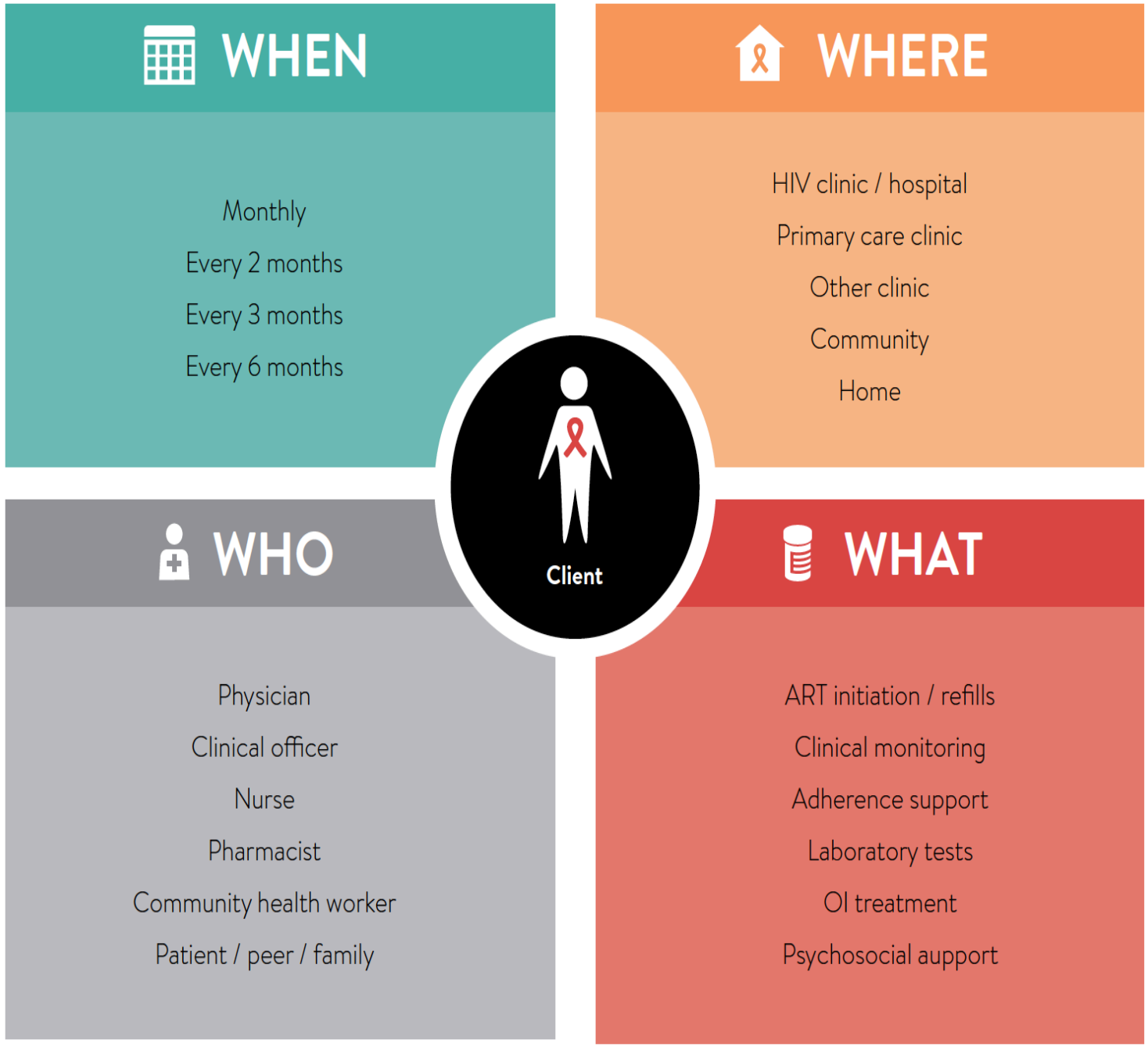
Differentiated service delivery

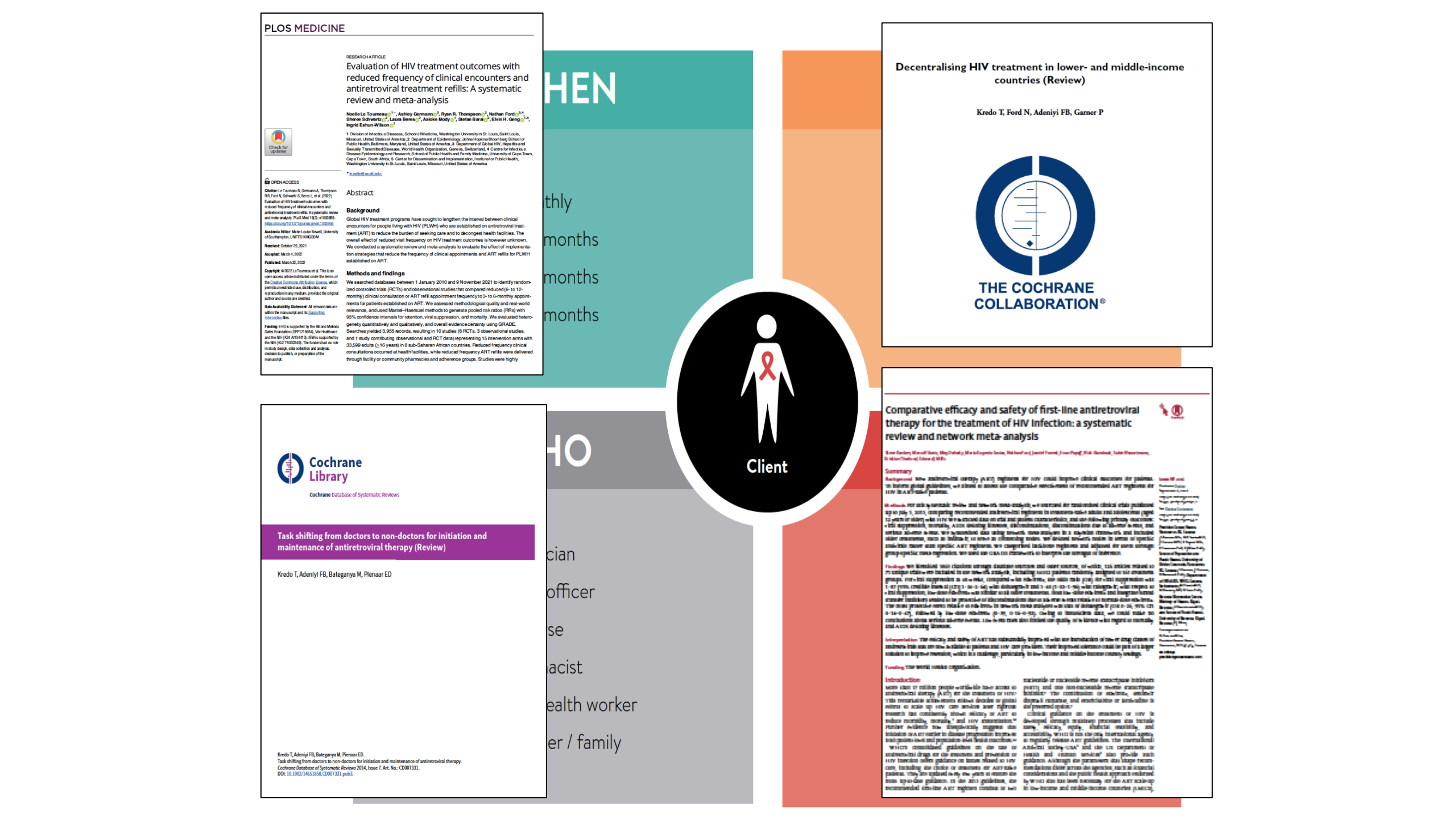
CLIENT PERSPECTIVE

- **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
Client
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 aupport


PLOS MEDICINE
RESEARCH ARTICLE
Evaluation of HIV treatment outcomes with reduced frequency of clinical encounters and antiretroviral treatment refills: A systematic review and meta-analysis
Noelle Le Tourneau, Ashley Germann, Ryan R. Thompson, Nathan Ford, Sheree Schwartz, Laura Beres, Asaloke Mody, Stefan Baral, Elvin H. Geng, Ingrid Eshun-Wilson
1 Division of Infectious Diseases, School of Medicine, Washington University in St. Louis, Saint Louis, Missouri, United States of America, 2 Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America, 3 Department of Global HIV, Hepatitis and Sexually Transmitted Diseases, World Health Organization, Geneva, Switzerland, 4 Centre for Infectious Disease Epidemiology and Research, School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa, 5 Center for Dissemination and Implementation, Institute for Public Health, Washington University in St. Louis, Saint Louis, Missouri, United States of America
Abstract
Background
Methods and findings
HEN
thly
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months
months
Client
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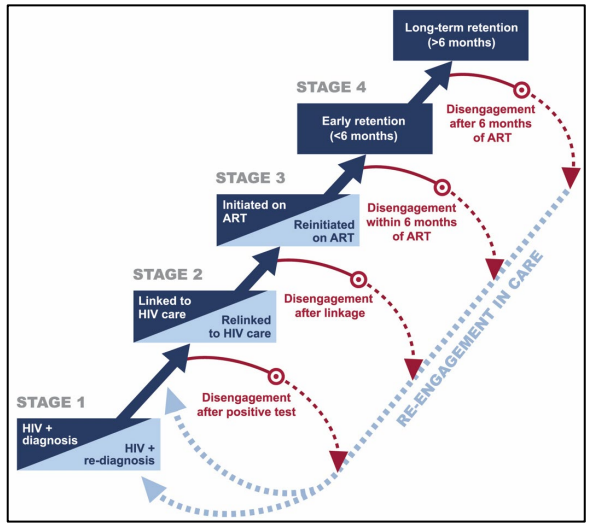
ealth worker
er / family
Decentralising HIV treatment in lower- and middle-income countries (Review)
Kredo T, Ford N, Adeniyi FB, Garner P
THE COCHRANE COLLABORATION®
Cochrane Library
Cochrane Database of Systematic Reviews
Task shifting from doctors to non-doctors for initiation and maintenance of antiretroviral therapy (Review)
Kredo T, Adeniyi FB, Bateganya M, Pienaar ED
Kredo T, Adeniyi FB, Bateganya M, Pienaar ED.
Task shifting from doctors to non-doctors for initiation and maintenance of antiretroviral therapy.
Cochrane Database of Systematic Reviews 2014, Issue 7. Art. No.: CD007331.
DOI: 10.1002/14651858.CD007331.pub3.
Comparative efficacy and safety of first-line antiretroviral therapy for the treatment of HIV infection: a systematic review and network meta-analysis
Summary
Introduction

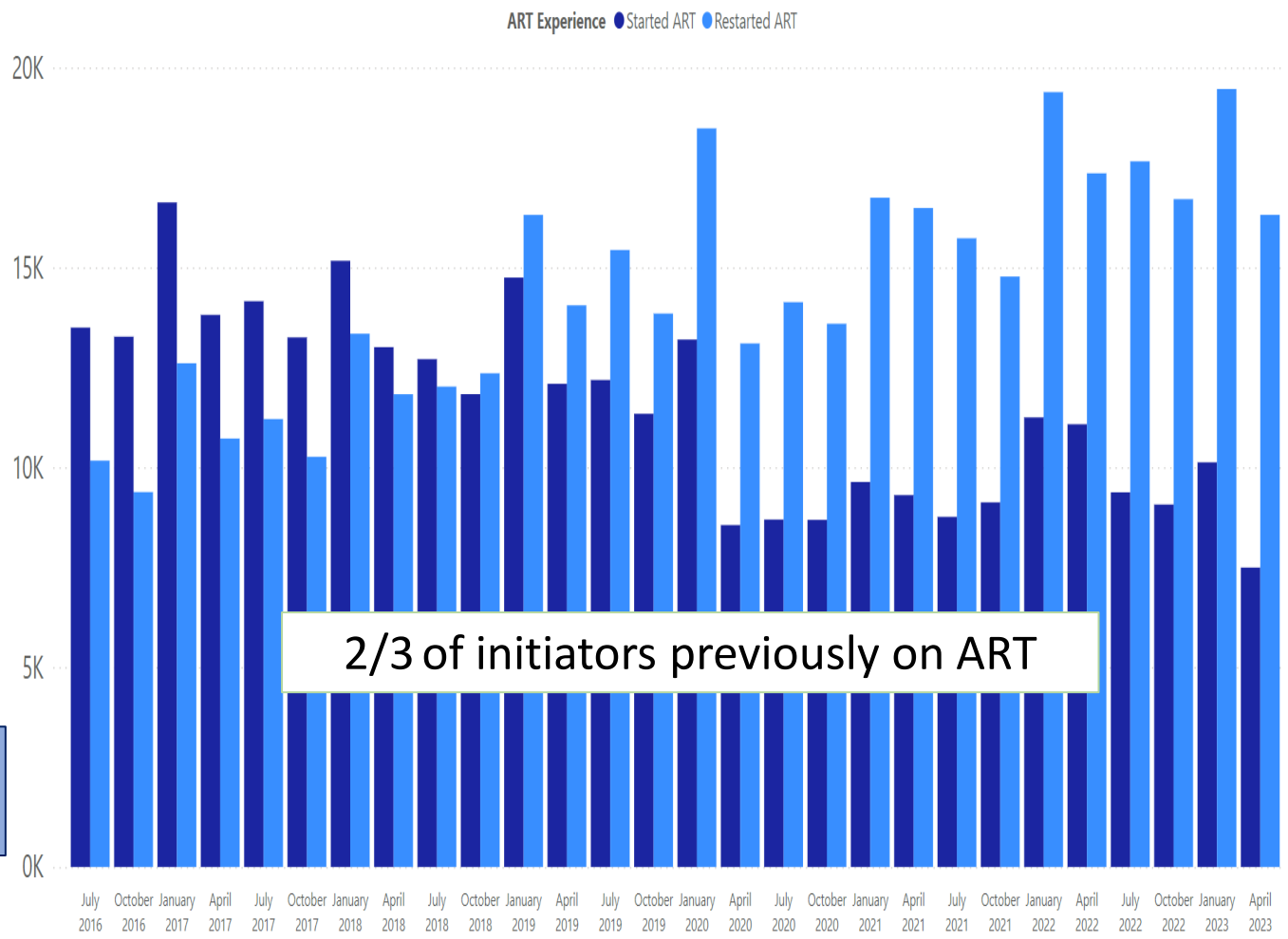
Increasingly, ART initiators are not treatment-naive



Ehrenkranz, Plos Med 2021

20-50% are reinitiating

Benade, BMJ Open 2023



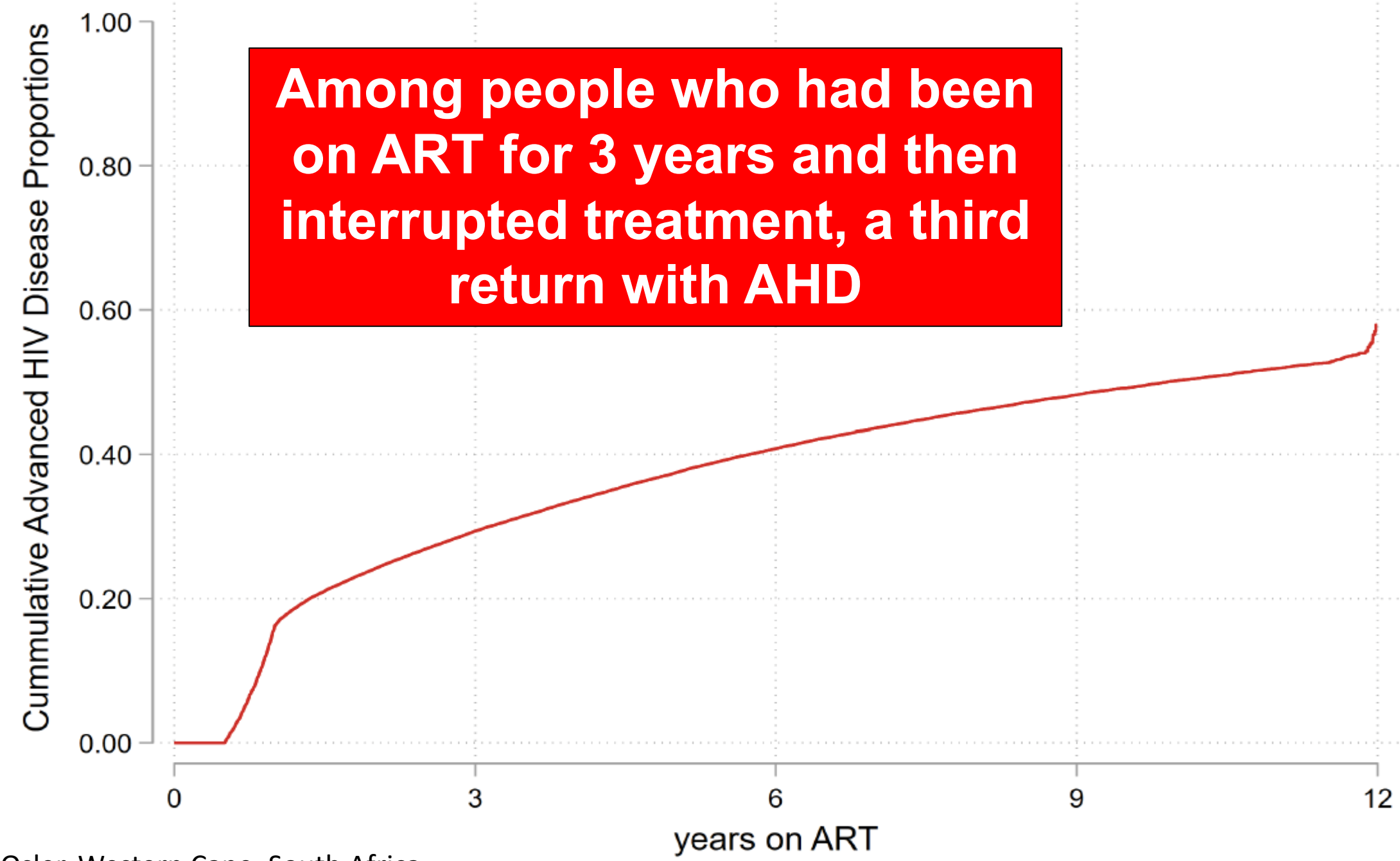
2/3 of initiators previously on ART

Retention & linkage to care

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

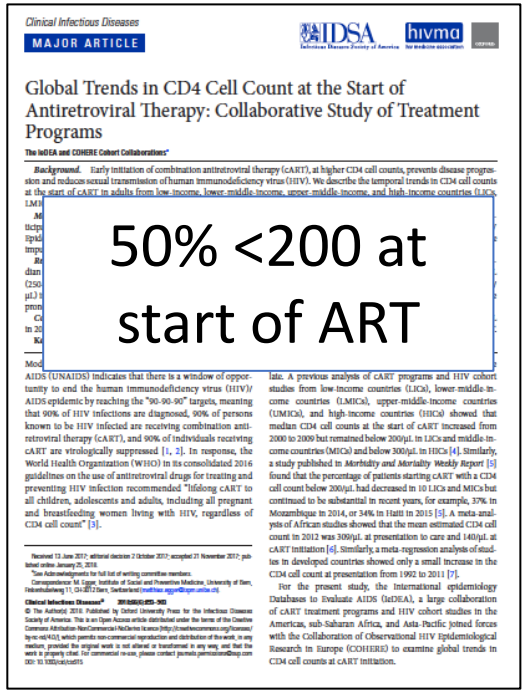
Gus Cairns | 11 May 2023

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.



Meg Osler. Western Cape, South Africa

Advanced HIV Disease



Clinical Infectious Diseases

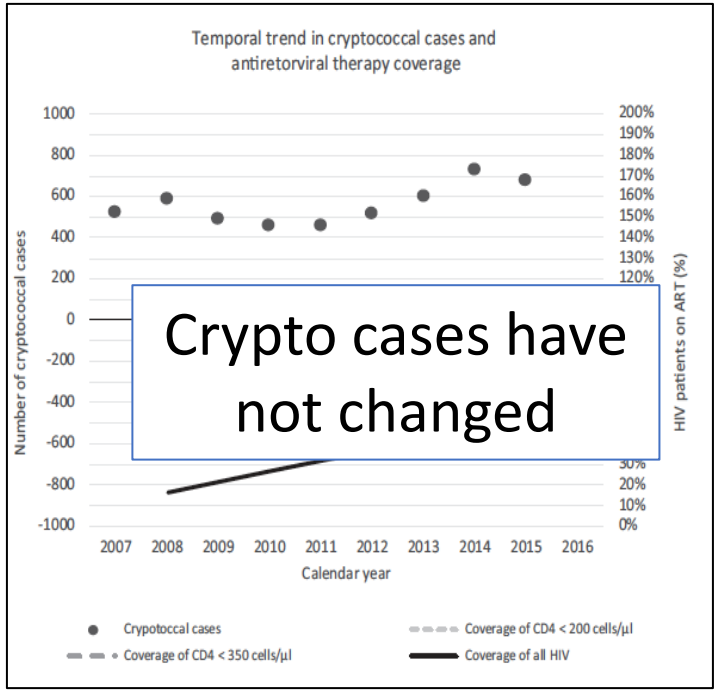
MAJOR ARTICLE

IDSA hivma

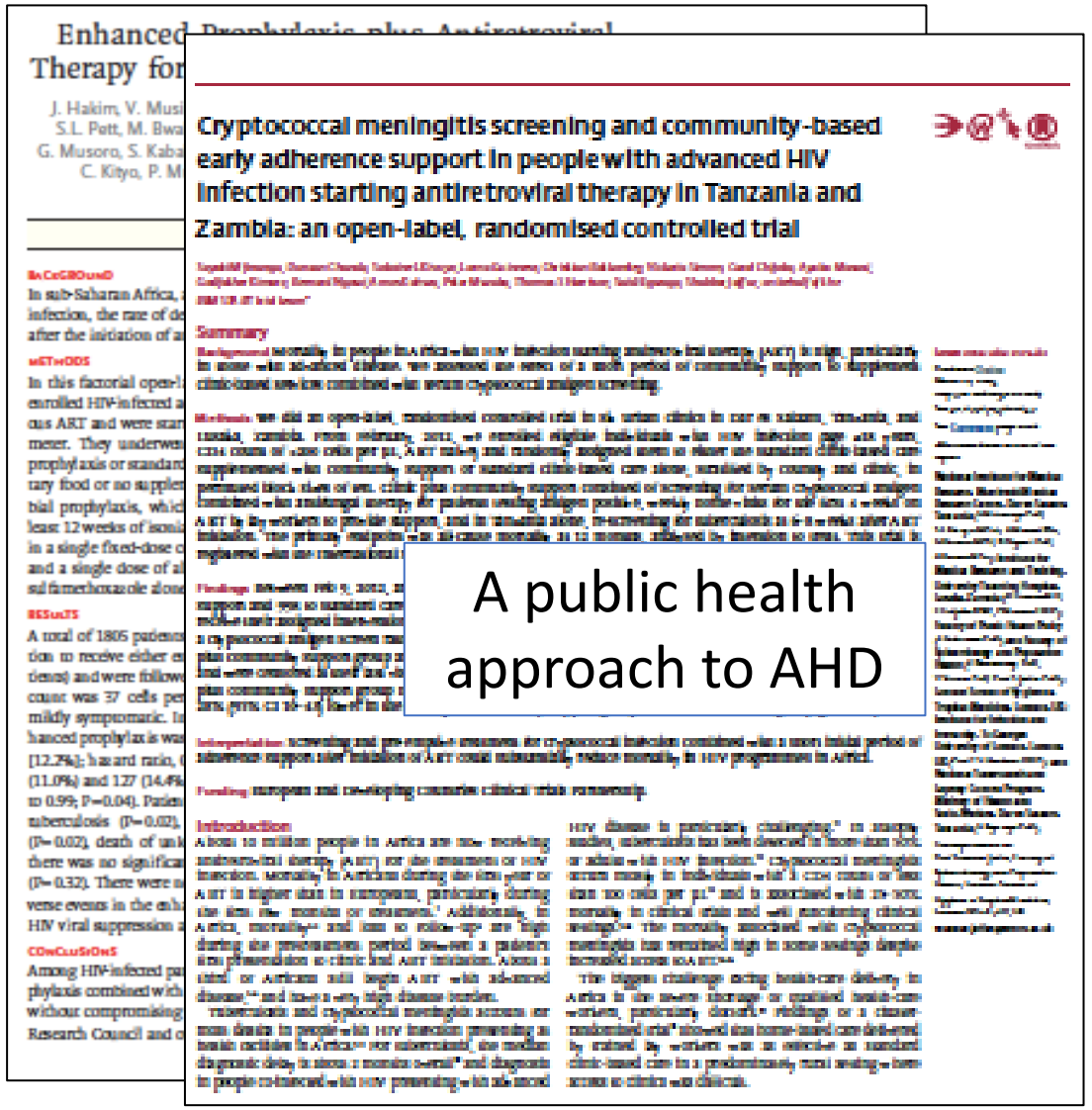
Global Trends in CD4 Cell Count at the Start of Antiretroviral Therapy: Collaborative Study of Treatment Programs

The IeDEA and COHERE Cohort Collaborators*

50% <200 at start of ART



Crypto cases have not changed



Enhanced Therapy for

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

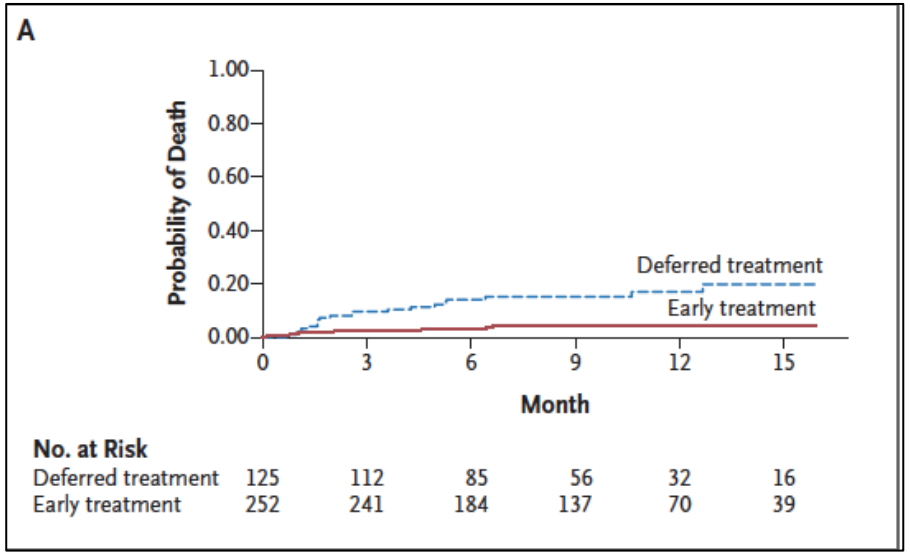
Summary

A public health approach to AHD

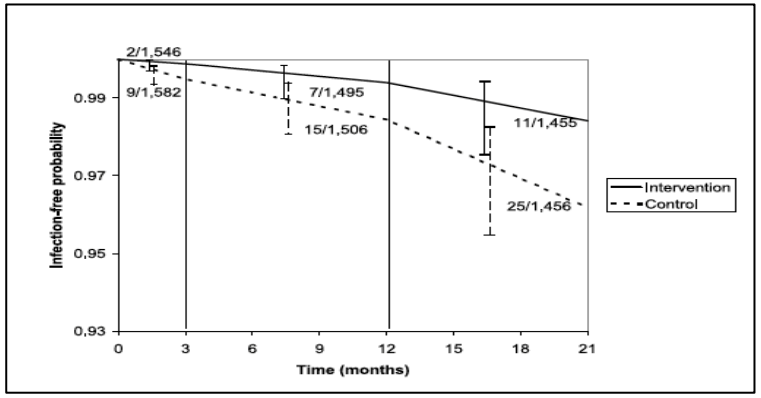
How evidence informs policy

Guideline development at WHO

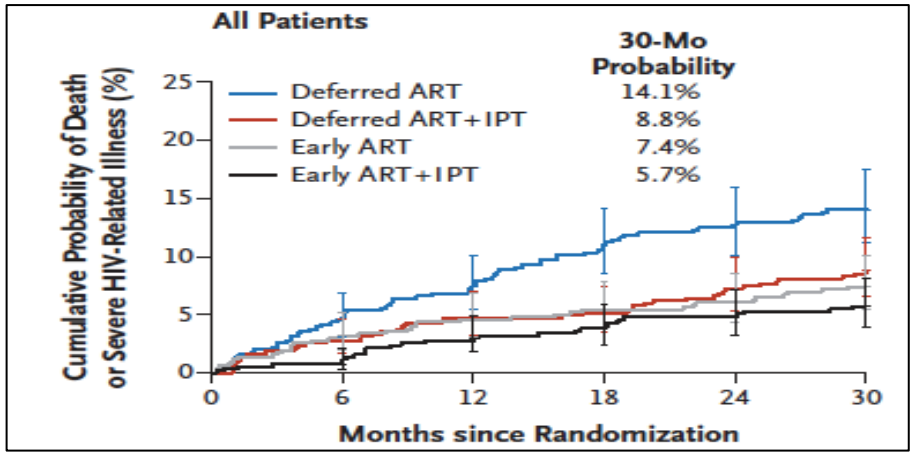
Trials can rapidly change policy and practice

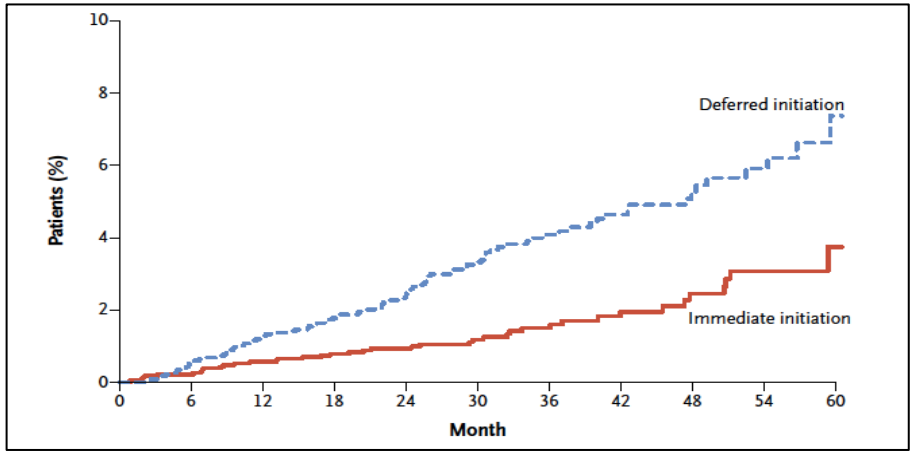


Violari, NEJM 2010



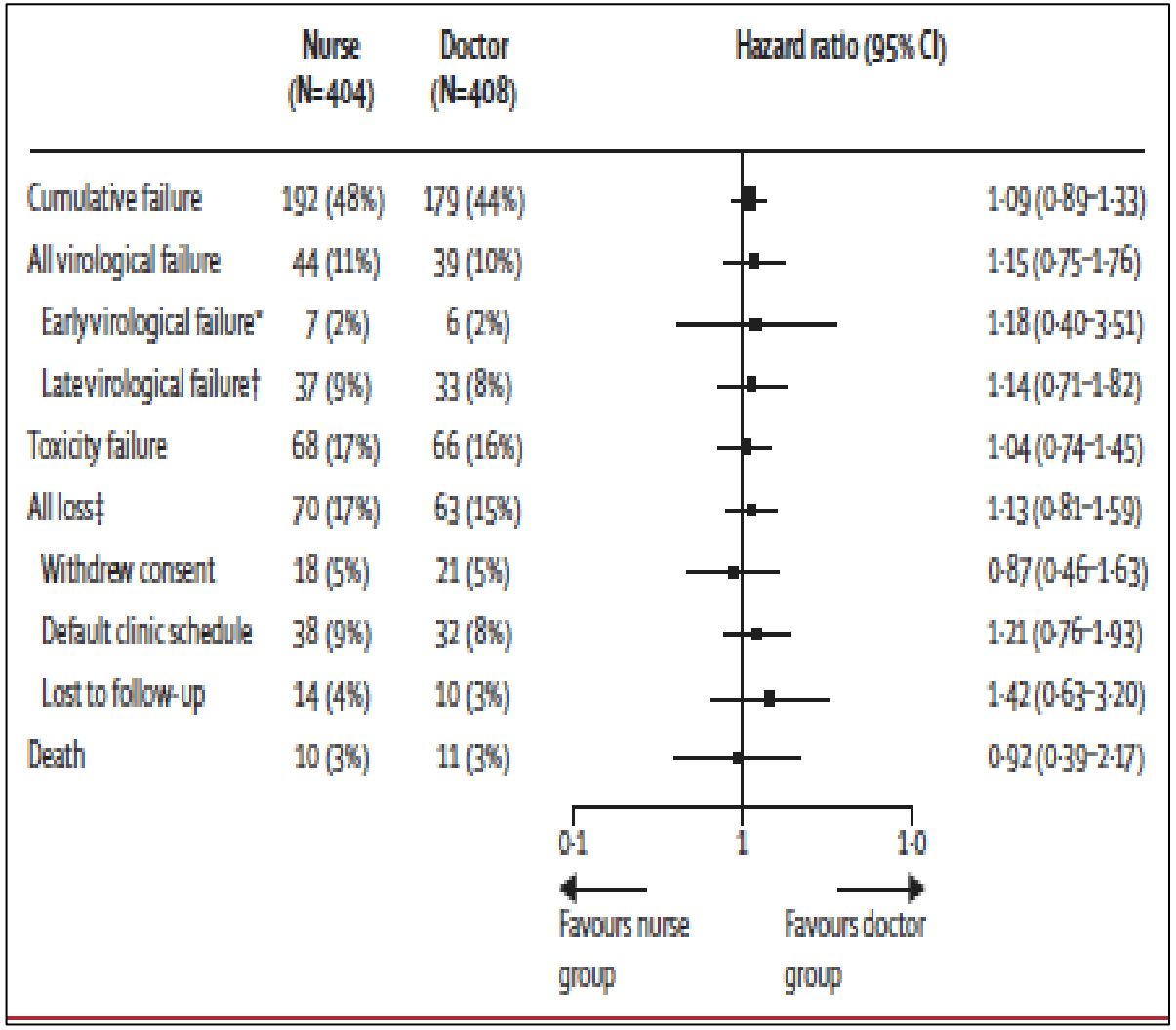
Auvert, Plos Med 2005





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

Use of evidence in WHO recommendations

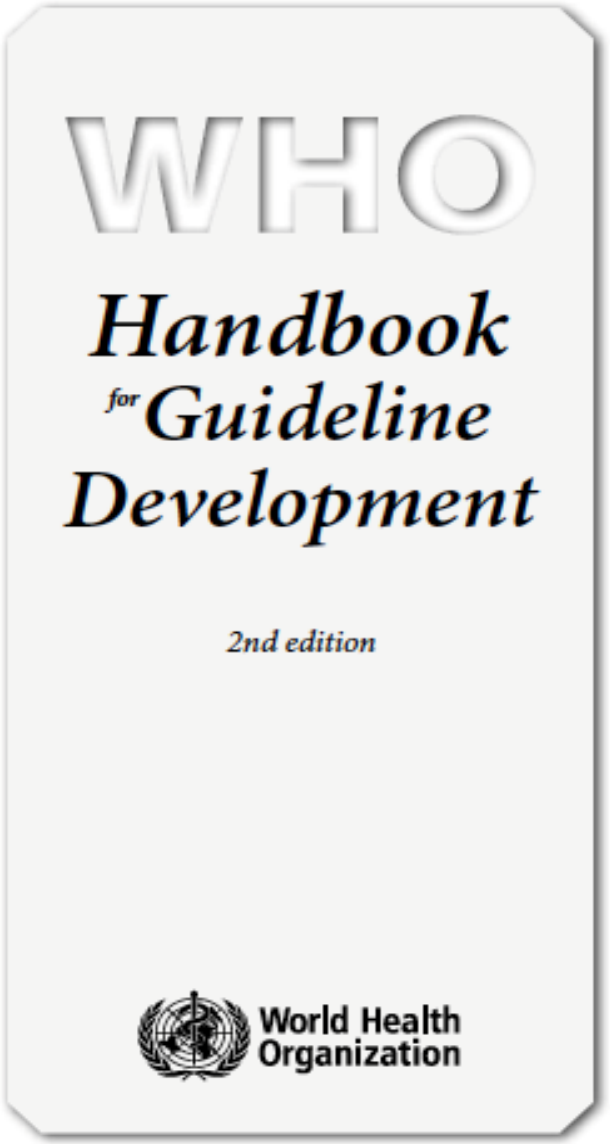
Summary

Introduction

Oxman, 2007

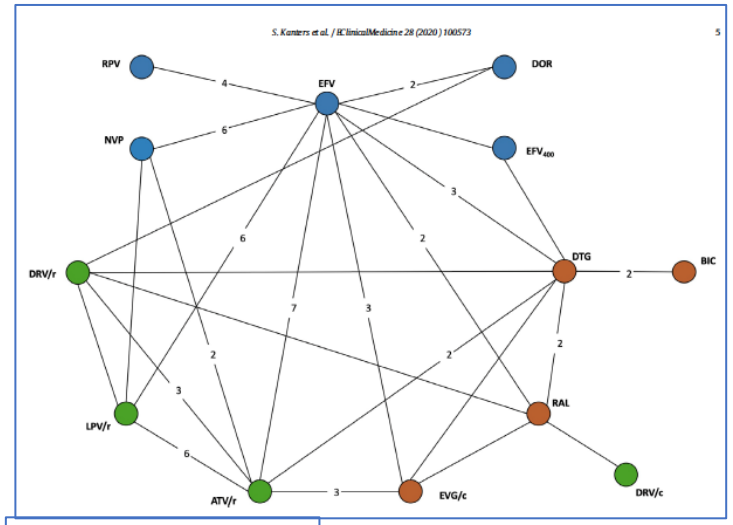
"Evidence is generally not retrieved, appraised, synthesised, and interpreted using systematic and transparent methods.

Processes rely heavily on experts"

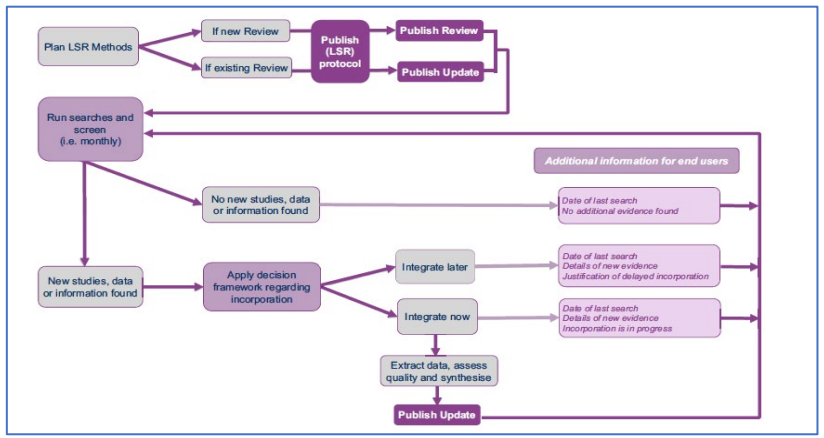


Evidence to decisions	
Safety and efficacy	RCTs, observational studies
Feasibility	Qualitative research; surveys
Acceptability	Qualitative research; surveys
Cost	Economic data; analyses
Values and preferences: provider & recipient	Qualitative research; surveys
Ethics, equity and Human rights	Qualitative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

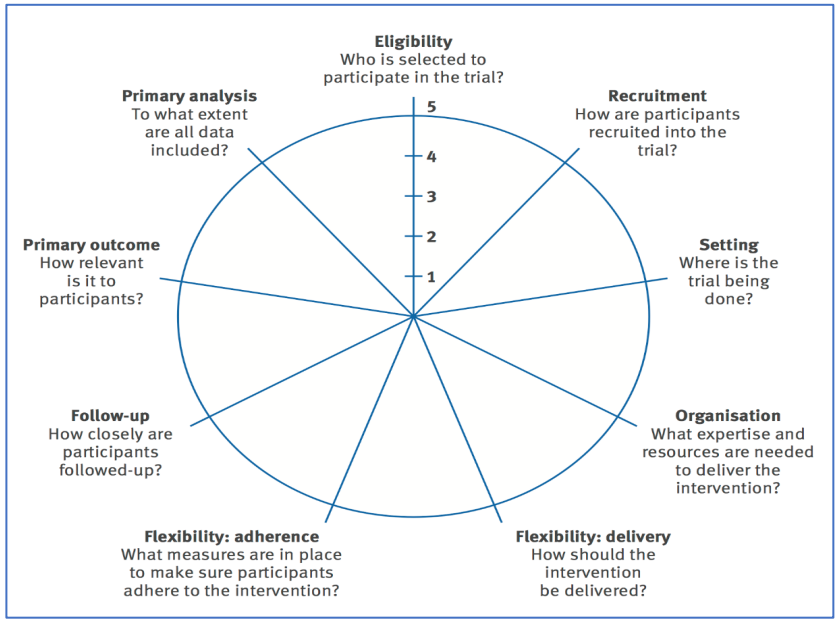
Future directions



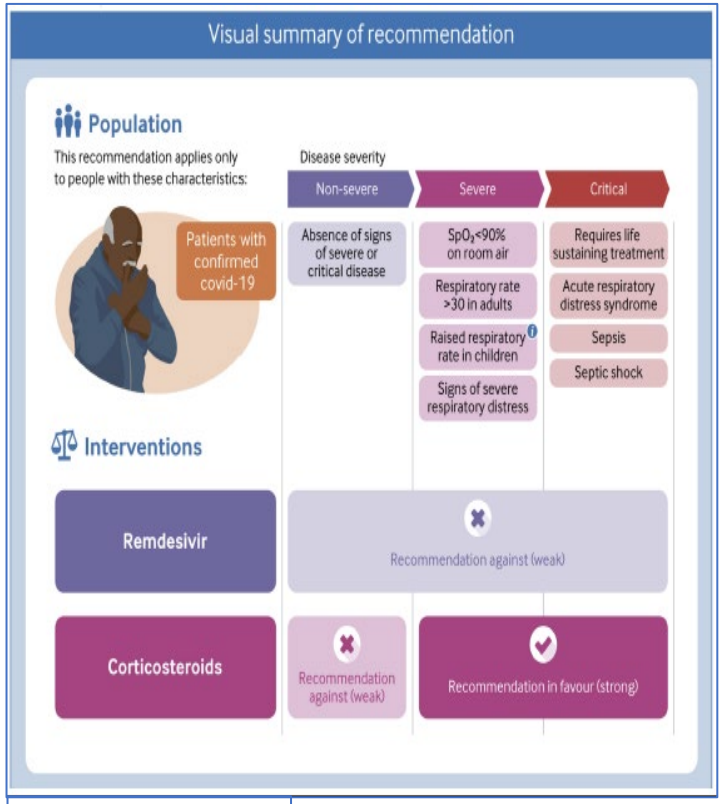
Kanters, EClinMed 2020



Elliott J Clin Epi 2017



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



Rochwerg 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 Ive, Jennifer Zeinecker, Marna Cornell, Christie Hellberg, Charlotte Ingram, Ravindre Panchia, Mohammed Rassool, René Gonin, Wendy Stevens, Hendré Truter, Marjorie Dehlinger, Charles van der, James McIntyre, Robin Wood, for the CIPRA-SA Study Team*

Summary

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

Methods This randomised non-inferiority trial was undertaken at two South African primary-care clinics. HIV-p individuals with a CD4 cell count of less than 350 cells per µL or WHO stage 3 or 4 disease were randomly as 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 p objective was a composite endpoint of treatment-limiting events, incorporating mortality, viral failure, treat limiting toxic effects, and adherence to visit schedule. Analysis was by intention to treat. Non-inferiority of the versus doctor group for cumulative treatment failure was prespecified as an upper 95% CI for the hazard rat was less than 1·40. This study is registered with ClinicalTrials.gov, number NCT00255840.

Findings 408 patients were assigned to doctor-monitored ART care and 404 to nurse-monitored ART ca participants were analysed. 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), whi within the limits for non-inferiority. After a median follow-up of 120 weeks (IQR 60–144), deaths (ten *vs* 11), viro failures (44 *vs* 39), toxicity failures (68 *vs* 66), and programme losses (70 *vs* 63) were similar in nurse and groups, respectively.

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

Funding National Institutes of Health; United States Agency for International Development; National Insti 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] Finding 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,[3–7] which could be an indicator of the complexities of HIV infection and its management.[8] By contrast with the small epidemic in resource-rich countries, there are 22·4 million people living with HIV in sub-Saharan Africa,[9] with an estimated 3·8 million in urgent need of treatment.[9] Globally, there is a shortage of 4·3 million health workers (doctors, midwives, nurses, and support workers);[9] in South Africa there are only 17·4 medical practitioners per 100 000 people, who are concentrated in urban areas.[10,11]

By contrast with the individualised approach t care in developed countries, WHO has proposed a health approach to antiretroviral therapy (ART) to scaling up of access to treatment for large numb HIV-positive adults and children in developing coun An approach using standardised simplified tre protocols and decentralised service delivery was dev to enable lower level health-care workers to deliver Models of care have investigated task shifting to officers[12] and a combination of nurses and comm workers;[13] however, nurse-led models of antiret delivery have been one of the most widely implem models of HIV care in poor-resourced African settin Findings from a trial have shown that work-site tre of hypertension by specially trained nurses significantly improved blood pressure control an adherence.[14] So far no randomised prospective stu been published to show the effectiveness of

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Clinical Infectious Diseases

VIEWPOINTS

IDSA Infectious Diseases Society of America | hivma hiv medicine association

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

Thomas S. Harrison,[1,2,3] David S. Lawrence,[4,5] Henry C. Mwandumba,[6,7,8] David R. Boulware,[9,10] Mina C. Hosseinipour,[11,12] Olivier Crasmo Mointjes,[13,14] Mosepele Mosepele,[6,15] and Joseph N. Jarvis[4,5,6]

[1]Institute of Infection and Immunity, St George's University London, London, United Kingdom; [2]Clinical Academic Group in Infection and Immunity, St George's University Hos London, United Kingdom; [3]Medical Research Council Centre for Medical Mycology, University of Exeter, Exeter, United Kingdom; [4]Department of Clinical Research, Fac Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom; [5]Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana; [6]Clinical Sci School of Tropical Medicine, Liverpool, United Kingdom; [7]Malawi-Liverpool-Wellcome Clinical Research Programme, Blantyre, Malawi; [8]Department of Medicine, Ka Sciences, Blantyre, Malawi; [9]Infectious Diseases Institute, College of Health Sciences, Makerere University, Kampala, Uganda; [10]Division of Infectious Diseases and University of Minnesota, Minneapolis, Minnesota, USA; [11]Lompoc Medical Relief Trust (University of North Carolina Project), Lilongwe, Malawi; [12]Department of M Carolina, Chapel Hill, North Carolina, USA; [13]Institut Pasteur, National Center for Scientific Research, Molecular Mycology Unit and National Reference Center for Invasi Unités Mixtes de Recherche 2000, Paris, France; [14]Université de Paris-Cité, Necker Pasteur Center for Infectious Diseases and Tropical Medicine, Hôpital Necker En Publique–Hôpitaux de Paris, IAU Imagine, Paris, France; [15]Wellcome Centre for Infectious Diseases Research in Africa, Institute of Infectious Disease and Molecular M Africa; [16]Department of Medicine, University of Cape Town, Cape Town, South Africa; and [17]Department of Internal Medicine, University of Botswana, Gaborone, Bo

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

Keywords. cryptococcal meningitis; HIV; amphotericin B; fluconazole; flucytosine.

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 [

we present an overview of the findings of th Therapy Induction Optimization (AMBITIO cuss their applicability to high-income setti in LMICs have historically been overlooked guidelines for of high-income countries. It is pare contexts, particularly when control regi trials differ from the standard of care in hig and when the ability to monitor and mana treatment-related complications varies, such ison of reported mortalities in high-income inappropriate. Nevertheless, we argue that data for novel treatment approaches from l domized, controlled trials provide critical insig and toxicity and options for treatment that are ble and should therefore be considered in hi We cover only HIV-associated cryptococcal m of other risk groups requires specific studies.

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Correspondence: J. N. Jarvis, Botswana Harvard AIDS Institute Partnership, Private Bag [redacted], Gaborone, Botswana (joseph.jarvis@lshtm.ac.uk).

Clinical Infectious Diseases® 2022;76(5):944–5

https://doi.org/10.1093/cid/ciac752

Short-Course Amphotericin-based Treatment for Cr

A program of clinical trials across sub-Saha tiated in 2004. The aim was to devel

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Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

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.

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