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FOR MANAGING ADVANCED HIV DISEASE AND RAPID INITIATION OF ANTIRETROVIRAL THERAPY

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ANNEXES

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Declaration of interests: guideline development group

	Country and WHO region	Employment/ consulting	Research support	Investment interests	Intellectual property	Public statements	Additional information	Tobacco products	Conflicts and management plan
Alexandra Calmy, Hôpitaux Universitaires de Genève (UHG)	Switzerland, EURO	0	Educational and research grants for the HIV service in UHG from ViiV,Janssen-Cilag, MSD, BMS: total amount USD 47,255	0	0	0	Travel grant to CROI conference 2017: USD 3,016	0	Travel grant financial, non-significant. Other funds go to HIV service not to individual Full participation
Alison Grant, London School of Hygiene and Tropical Medicine	UK, EURO	0	0	0	0	0	0	0	No conflict. Full participation
David Lalloo, Liverpool School of Tropical Medicine	UK, EURO	0	EDCTP funding to research unit: 1.2 million USD. MRC grant to research unit: 1.8 million USD, Wellcome research trust: 2.3 million USD	0	0	0	0	0	No conflict. Full participation
Di Gibb, Medical Research Council	UK, EURO	Member of ViiV healthcare advisory board	0	0	0	0	Principal investigator of REALITY trial, key clinical trial in systematic review of packaged interventions	0	Membership of advisory board not funded and unrelated to guideline topic Partial exclusion: exclude from formulation of recommendations on packaged interventions
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Nandi Siegfried, independent methodologist	South Africa, AFRO	0	0	0	0	0	0	0	No conflict. Full participation
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Tom Chiller, CDC	USA, AMRO	0	0	0	0	0	0	0	No conflict. Full participation

Declaration of interests: external review group

Name, institution	Country and WHO region	Employment / consulting	Research support	Investment interests	Intellectual property	Public statements	Additional information	Tobacco products	Conflicts and management plan
Xavier Anglaret **Inserm – French National Institute of Health and Medical Research**	France, EURO	0	Research grant from ANRS France for the research unit	0	0	0	0	0	No conflict of interest identified. Consider all comments
Moherndran Archary **King Edward VIII Hospital**	South Africa AFRO	0	0	0	0	0	0	0	None. Consider all comments
Moses Bateganya **CDC**	USA/Uganda AMRO/AFRO	0	0	0	0	0	0	0	None. Consider all comments
David Boulware **University of Minnesota**	USA/Uganda AMRO/AFRO	0	0	0	0	0	0	0	None. Consider all comments
Sergio Carmona **NHLS**	South Africa	0	Research Unit: Assay RnD or optimization for local patient population [Roche]; Assay RnD and CE for qualitative HIV assay (p/t research assistant and reagents)[Cepheid]; DBS viral load assay optimization [Abbott] Research Unit:Technical advisory board CROI 2014 [Roche]; Speaker IAS 2014 [Abbott]; Speaker:Infectious Disease Symposium Asia Pacific (Travel only; No honorarium accepted). [Roche]	0	0	0	0	0	Significant research support. Comments interpreted in the context of declared conflicts of interest
Marcelo Freitas **ICAP Mozambique**	Mozambique AFRO	0	0	0	0	0	0	0	None. Consider all comments
Beatriz Grinsztejn **Fiocruz**	Brazil AMRO	0	0	0	0	0	0	0	None. Consider all comments

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David Meya **Makerere University, Kampala, Uganda**	Uganda AFRO	0	0	0	0	0	0	0	None. Consider all comments
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Packaged interventions for people presenting with advanced HIV disease.

A systematic review

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Background

Despite significant progress in scaling up access to antiretroviral therapy (ART) globally and a progressive shift towards starting ART at higher CD4 cell counts, an important proportion of HIV positive patients continue to present to health services when they are already at an advanced stage of disease[1]. Patients presenting with advanced HIV disease are defined by World Health Organization (WHO) as those with a CD4 count <200 cells/mm^3 or WHO Clinical Stage 3 and 4 defining illness at presentation [2]. Mortality is high among patients presenting with advanced HIV disease, including among those starting ART in the first 3 months after ART initiation. Causes of death are multiple, with co-infections such as TB, cryptococcal meningitis, severe bacterial infections and immune reconstitution inflammatory syndrome (IRIS) playing a prominent role [3-5].

Estimates suggest that around 25% of patients initiating ART globally do so with a CD4 < 100 cells/mm^3 [6] . In sub-Saharan Africa, in particular, advanced HIV disease at presentation remains a major challenge. An analysis from four sub-Saharan African countries carried out in in 2011 reported that 35% of patients had CD4 cell counts < 100 cells/mm^3 at the time of initiation of ART[7] . A meta-regression of systematic review data from sub-Saharan African countries reported that in 2013, the mean CD4 cell count in HIV patients at the time of initiation of ART was 140 cells/mm^3. This analysis also found that there was no evidence of a change in trend of CD4 counts at presentation between 2002 and 2013.The review concluded that despite increased access to ART in recent years, barriers to presentation, diagnosis, and linkage to HIV care remain major challenges that require attention if the population-level benefits of ART are to be maximised[1].

A number of interventions in addition to ART are already recommended in WHO guidelines for patients presenting with advanced HIV disease to reduce mortality and morbidity. Interventions currently recommended include isoniazid preventative therapy (IPT) to prevent TB, co-trimoxazole prophylaxis, screening for cryptococcal disease in adults with CD4 counts <100 cells/mm^3 in settings with a high prevalence of cryptococcal antigenaemia in these patients [8, 9,10] and screening for TB using urine LAM[11].

Recent studies have assessed the potential for enhanced packages of interventions to reduce mortality/morbidity in patients presenting with advanced HIV disease, given in addition to standard care already recommended by WHO guidelines.

Objectives

The aim of this review was to determine if packaged interventions, which include enhanced infection prophylaxis, screening, and other elements of care delivered together, can improve outcomes in HIV-positive patients presenting with advanced disease.

Methods

Study Selection

We included randomized control trials (RCTs). The study population included was HIV-positive patients presenting with advanced disease defined as CD4 count < 200 cells/mm^3 and/or WHO Stage 3/4 disease[2]. Studies that used a different definition of advanced disease (e.g. CD4 <100 cells/mm^3) were included provided the population falls within the definition of advanced disease. The interventions included were intervention packages (two or more interventions) designed to be delivered together to patients presenting with advanced disease with the aim of reducing mortality and/or severe morbidity.

Types of outcome measures

We analysed the following outcomes: all-cause mortality, incident morbidity, hospitalisations, serious adverse events, CD4 cell gain and ART adherence.

Search Strategy

We conducted the search for eligible studies from using search terms in English following PRISMA guidelines for reporting of systematic reviews[5]. The following electronic databases were searched: PubMed, MEDLINE, EMBASE, Cochrane library and Clinicaltrials.gov, from inception to September 2016. Conference proceedings of the International Aids Society Conference (IAS) were searched from 2012-2016 and Conference on Retroviruses and Opportunistic Infections (CROI) were searched from 2014-2016 (CROI abstracts for 2102 and 2013 were not available). Standard search terms for HIV Infection were combined with the following terms: severe immunodeficiency OR severe immunodeficiency [tiab] OR severe immun*[tiab] OR advanced disease [tiab] OR late presenters [tiab] OR late presentation [tiab] OR delayed diagnosis [tiab] OR delayed access to care [tiab] OR CD4 200 [tiab] OR CD4 100 [tiab] OR CD4 50 [tiab]. Screening of abstracts was carried out in duplicate independently by two reviewers.

Studies were excluded if they contained only one intervention. Only two studies were identified which fitted the inclusion criteria. Both were open-label RCTs.

Certainty of the evidence

Two reviewers assessed risk of bias using the Cochrane Risk of Bias Tool[12]. This information was included into the overall GRADE (Grading of Recommendations Assessment, Development and Evaluation) assessment of the certainty of the evidence[13].

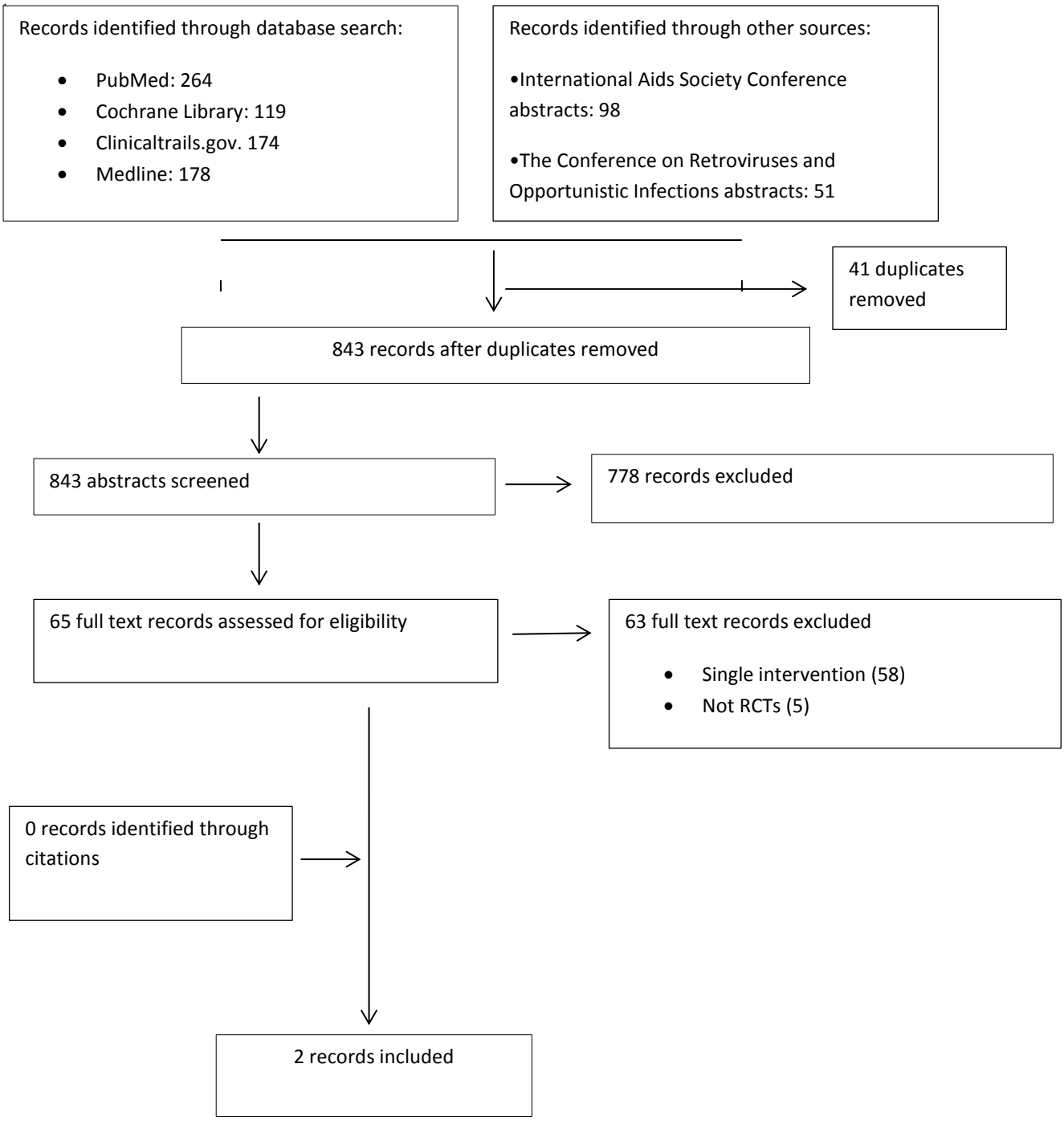
Data extraction/analysis

Data were extracted by one reviewer (CM) and verified by a second reviewer (NF). Because of differences between interventions included in the enhanced package of care in the included studies, data were not pooled.

Results

Included studies

Two reviewers independently screened 843 abstracts, for eligibility. Sixty five full text articles were reviewed. One of the studies was identified via conference abstracts and the full text article (pre-publication) was obtained through the authors. The PRISMA flow diagram of the study selection for inclusion in the systematic review is shown in Figure 1.



PRISMA flow diagram of study selection for inclusion in systematic review

[1] Abstracts from The Conference on Retroviruses and Opportunistic Infections were available for 2014-2016 only.

Description of included studies

We identified two RCTs for inclusion in the review. In both trials patients who had previously received ART were excluded. In the REMSTART trial patients were selected from ambulatory care, while in the REALITY study hospitalised patients were included. Characteristics of included studies are shown in table 1.

Study 1: Mfinanga S, Chanda D, Kivuyo SL, et al. 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. Lancet. 2015;385(9983):2173-2182.

In the first trial, carried out in Tanzania and Zambia [14], adult patients aged 18 years and over with advanced HIV disease (CD4<200 cells/mm^3) were randomized to an enhanced package of interventions or standard care.

Intervention

Those in the enhanced package of care group underwent a serum cryptococcal antigen test (CrAg) using a novel serum antigen assay. If this test was positive they were offered a lumbar puncture to screen for cryptococcal meningitis. Those found to have cryptococcal meningitis were treated with amphotericin B for 14 days followed by oral fluconazole for at least 8 weeks. Those testing CrAg positive but who had a negative lumbar puncture or who refused lumbar puncture were treated with oral fluconazole for 10 weeks (800mg per day for 2 weeks followed by 400mg per day for 8 weeks).

Participants in the enhanced package also underwent screening for pulmonary TB using sputum Gene Xpert MTB/RIF regardless of symptoms and all received ART which was started within 14 days. Those who screened negative for CrAg received ART immediately, while ART was delayed by two weeks in those who screened positive for CrAg or Gene Xpert MTB/RIF in accordance with national guidelines.

Participants in the enhanced package of care group had weekly visits for the first 4 weeks on ART by lay workers to provide support. Visits took place at home or a nearby location of the participants' choice. In Tanzania, re-screening for tuberculosis at 6–8 weeks after ART initiation also took place.

Control

Those in the control group received standard of care and all received ART which was started within 14 days. They also underwent screening for pulmonary TB using sputum Gene Xpert MTB/RIF regardless of symptoms and if positive ART was delayed in accordance with national guidelines.

Outcomes

All-cause mortality at 12 months, hospitalizations, ART adherence and costs to the health service were compared between the two groups.

<u>Study 2:</u> Hakim J, Musiime V, Szubert AJ, et al. Enhanced prophylaxis with antiretroviral therapy for advanced HIV in Africa. 2017 (pre-publication).

In the second trial[15], carried out in centres in Malawi, Uganda, Zimbabwe and Kenya, outcomes were compared in children ≥5 years and adults with CD4 cell counts <100 cells/mm^3 randomized to either standard care or an enhanced package of prophylaxis. This study was a factorial trial. Additional interventions introduced were supplementary food and additional raltegravir. Neither of these two interventions was found to improve outcomes and were not taken forward for our review.

Intervention

Participants in the intervention group received ART, a fixed-dose combination (FDC) of co-trimoxazole 800/160mg/isoniazid 300mg/pyridoxine 25mg as a once daily scored tablet and an enhanced package of prophylaxis which included fluconazole 100mg once daily for 12 weeks, azithromycin 500mg once daily for 5 days and single dose albendazole 400mg. Doses were halved for children aged 5≤13 years. After 12 weeks, fluconazole was stopped and the FDC of co-trimoxazole/isoniazid/pyridoxine was continued or patients were switched to co-trimoxazole depending on national guidelines. All patients underwent symptomatic screening for active TB at enrolment using a symptom checklist with sputum examination and chest-x-ray if indicated.

Control

People in the standard care group received ART and co-trimoxazole 800/160mg for 12 weeks. After 12 weeks, they either continued ART and co-trimoxazole, or co-trimoxazole was switched to the daily FDC of co-trimoxazole/isoniazid/pyridoxine. In Malawi where isoniazid was not recommended in national guidelines co-trimoxazole only was continued. All patients underwent symptomatic screening for active TB at enrolment using a symptom checklist with sputum examination and chest-x-ray if indicated.

Outcomes

The primary end point was all-cause mortality at 24 weeks. Secondary outcomes included all-cause mortality at 48 weeks, new hospitalisations, new TB infections, new cryptococcal meningitis, new severe bacterial infections, serious adverse events, ART adherence, and CD4 cell gain. Outcomes of new infections and serious adverse events were assessed by an independent end-point review committee.

Analysis

Because of the heterogeneous nature of the interventions included in the enhanced package of care in the included studies, data extraction and analysis was carried out separately for both studies.

Table 1: Characteristics of included studies

Study	Setting	Sample	Design	Time frame	Population	Eligibility	Exclusions	Intervention	Control
Hakim et al. REALITY	Kenya, Malawi, Uganda, Zimbabwe	N= 1805 Adults=1733(96%) Children/adolescents=72 (4%)	Open-label RCT	June 2013-April 2015	Adults and children ≥5 years	CD4<100 cells/mm^3 at presentation ART naïve	Previously on ART Pregnant or breast feeding Hx of single dose nevirapine (PMTCT) Contraindications to drugs	ART and enhanced prophylaxis[2]: FDC of co-trimoxazole 800mg/160mg /INH 300mg/B6 25mg once per day x 12 weeks[2] Fluconazole100 mg/day x 12 weeks Azithromycin 500mg/day x 5 days Albendazole 400mg x single-dose After 12 weeks fluconazole stopped and either FDC of co-trimoxazole/INH/B6 continued or co-trimoxazole alone continued	ART and Co-trimoxazole for 12 weeks. After 12 weeks, either co-trimoxazole continued[3] or switched to FDC co-trimoxazole/INH/B6 300/25mg/day
Mfinanga et al. REMSTART	Zambia, Tanzania	1999	Open-label RCT	Feb 2012 – Sept 2013	Adults ≥18 years	CD4<200 cells/mm^3 at presentation ART naïve	Previously on ART Requiring immediate hospital admission	"Rapid"ART (median within 14 days) and standard care plus: Screened with novel CrAg test and offered antifungal treatment if antigen positive Weekly visits by trained workers either home, or to nearby locations for 4 weeks. Sputum GeneXpert assay irrespective of symptoms at baseline and at 6 weeks	"Rapid" ART (median within 14 days) and • Standard care as per national guidelines[4] Sputum GeneXpert assay irrespective of symptoms at baseline

[2] Doses were halved for children aged 5-<13 years
[3] In Malawi control group did not receive INH as not in national guidelines
[4] Standard care not defined in the study

Assessment of risk of bias in included studies

The overall risk of bias was rated to be low for both studies (Figure 2).

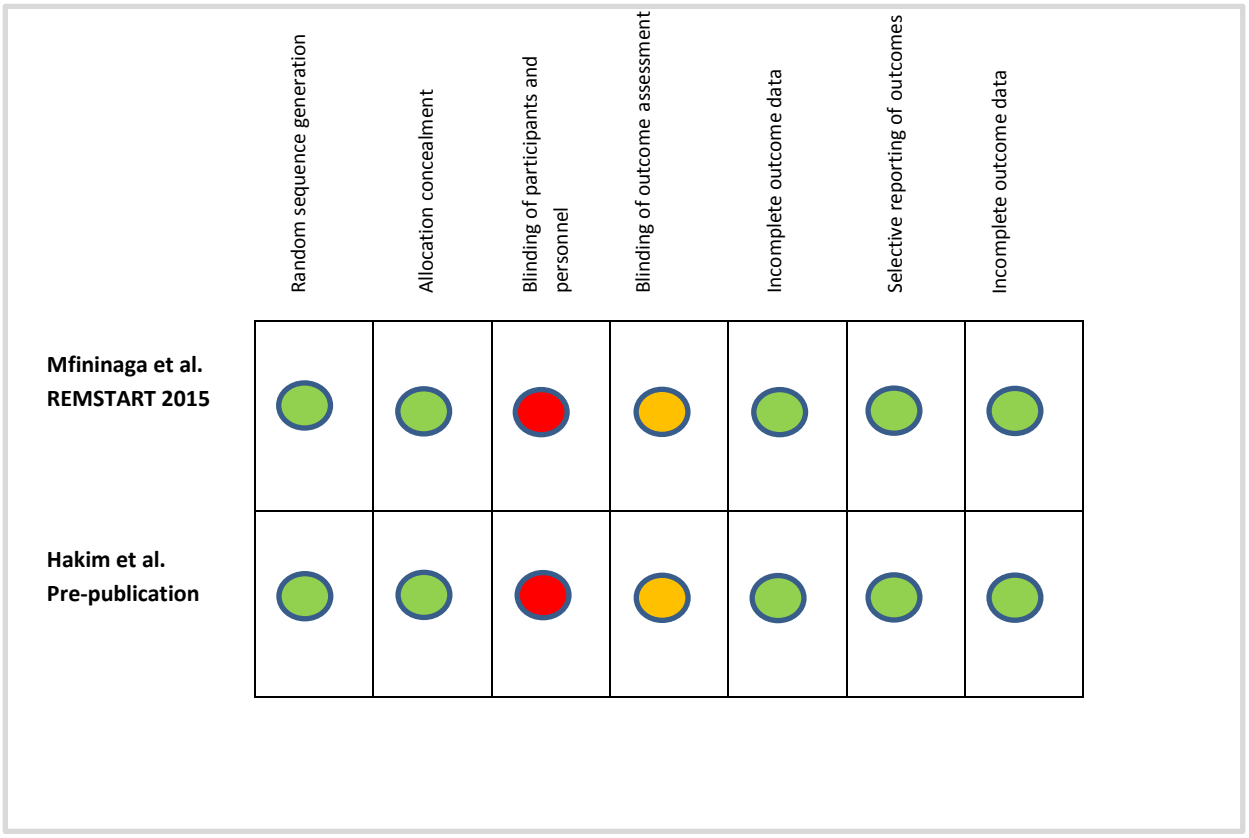


Figure 2: Risk of bias of included studies

Evidence summaries

Mortality

Both trials reported all-cause mortality. The overall certainty of evidence from both studies was high. In the REALITY trial, all- cause mortality was lower in the intervention (enhanced prophylaxis) group at 24 weeks (HR 0.73, 95% CI 0.55-0.98) and at 48 weeks (HR 0.76, 95%CI 0.58-0.99).

In the REMSTART trial, all-cause mortality at 12 months for those in the intervention group was also decreased: the adjusted RR was 0.72 (95% CI0.57-0.90) for the intervention group when compared with standard care, adjusted for study site, age, sex and baseline CD4 cell count.

Stratified analysis by age

Sub-groups analysis was carried out by age in the REALITY trial. Only 40 of the participants were aged 5 ≤13 years and there were no deaths in the standard group and only one death in the intervention group. Evidence was downgraded to low due to serious imprecision. In those aged >13 years, mortality was lower in the intervention group (HR 0.72, 0.54 to 0.97).

Stratified analysis by CD cell count.

REALITY trial: there was no evidence of a difference in mortality according to CD4 cell count when analysed as a continuous variable between the enhanced prophylaxis group and the control group (data not shown).

Hospitalisation

Both studies reported on hospitalizations. The certainty of the evidence was rated as high. In the REALITY trial the risk of new hospitalisations decreased in the intervention group: HR 0.82 (95% 0.68 to 0.99). In the REMSTART trail there was no difference in the risk of new hospital admissions between the intervention and control group (RR 1.02, 95% CI 0.74-1.41).

Incident morbidity

The REALITY trail reported on the number of new serious infections in both groups, assessed by and end-point review committee, blinded to allocation of participants. The certainty of the evidence was high. The hazard of new TB disease cases was lower in the intervention group (HR 0.69, 95%CI 0.51-0.94). The hazard of new cryptococcal disease cases were also reduced (HR 0.39, 95%CI 0.18-0.83). There was no difference in the hazard of new severe bacterial infections (HR 1.26, 95%CI 0.81-1.97).

Serious adverse events

The number of severe adverse events was assessed by the REALITY trial only. Assessed by an end-point review committee, there was no difference in the risk of serious adverse events (HR 0.86, 0.73-1.02). The certainty of the evidence was rated as high.

Adherence to ART

Both studies reported on ART adherence. REALITY at 24 and 48 weeks, and REMSTART at 6 and 12 months. For both studies ART adherence was self-reported by participants: (any missed doses in previous four weeks /1 month). The overall quality of evidence was moderate, downgraded due to risk of bias as a result of not blinding of outcome assessment and subjective outcome assessment.

The REALITY trial found no difference in self-reported ART adherence between both groups: RR of adherence in the intervention group was 1.01 (95%CI 0.98-1.03) at 24 weeks and RR 0.98 (95%CI 0.96-1.10) at 48 weeks. The REMSTART trial found a difference in adherence favouring the intervention at 6 months (RR 1.05, 95%CI 1.00-1.10), but not at 12 months (RR 0.99, 95% CI 0.95-1.04 at 12 months).

CD4 cell gain

CD4 cell gain was reported by the REALITY trial. The certainty of the evidence was high. Mean CD4 cell gain in the intervention group at 24 weeks was +113cells/$mm^{3,}$ (95%CI 112.7-113.2, SD+/- 3.1) and +112 cells/mm^{3}(95%CI 111.7-112.2, SD+/- 3.1) in the control groups (p=0.85).

Tables 2 and 3 summarize the GRADE assessment of the certainty of the evidence.

GRADE Table: REALITY trial

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Enhanced prophylaxis**	**standard care**	**Relative (95% CI)**	**Absolute (95% CI)**		
All-cause mortality at 24 weeks (follow up: 24 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	80/908 (8.8%)	108/899 (12.0%)	**RR 0.73** (0.55 to 0.98)	**32 fewer per 1,000** (from 2 fewer to 54 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
All-cause mortality at 24 weeks: subgroup analysis: Age 5-<13 years												
1	randomised trials	not serious	not serious	not serious	very serious a	none	1/26 (3.8%)	0/14 (0.0%)	not estimable		⊕⊕◯◯ LOW	CRITICAL
All-cause mortality at 48 weeks (follow up: 48 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	98/908 (10.8%)	127/899 (14.1%)	**HR 0.76** (0.58 to 0.99)	**32 fewer per 1,000** (from 1 fewer to 57 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Hospitalisations (follow up: 48 weeks; assessed with: End-point review committee)												
1	randomised trials	not serious	not serious	not serious	not serious	none	154/908 (17.0%)	186/899 (20.7%)	**HR 0.82** (0.68 to 0.99)	**34 fewer per 1,000** (from 2 fewer to 61 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

GRADE Table: REALITY trial

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Enhanced prophylaxis**	**standard care**	**Relative (95% CI)**	**Absolute (95% CI)**		
New TB disease (follow up: 48 weeks; assessed with: End point review committee)												
1	randomised trials	not serious	not serious	not serious	not serious	none	64/908 (7.0%)	92/899 (10.2%)	**HR 0.69** (0.51 to 0.94)	**31 fewer per 1,000** (from 6 fewer to 49 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
New cryptococcal disease (follow up: 48 weeks; assessed with: End point review committee)												
1	randomised trials	not serious	not serious	not serious	not serious	none	9/908 (1.0%)	23/899 (2.6%)	**HR 0.39** (0.18 to 0.83)	**16 fewer per 1,000** (from 4 fewer to 21 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
New presumptive severe bacterial infection (follow up: 48 weeks; assessed with: End point review committee)												
1	randomised trials	not serious	not serious	not serious	not serious	none	42/908 (4.6%)	33/899 (3.7%)	**HR 1.26** (0.81 to 1.97)	**9 more per 1,000** (from 7 fewer to 34 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Serious adverse events (follow up: 48 weeks; assessed with: End point review committee)												

GRADE Table: REALITY trial

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Enhanced prophylaxis**	**standard care**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	not serious	not serious	not serious	not serious	none	191/908 (21.0%)	219/899 (24.4%)	**HR 0.86** (0.73 to 1.02)	**30 fewer per 1,000** (from 4 more to 59 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
ART adherence (follow up: 24 weeks; assessed with: self-reported (not missing any doses of drugs in last 4 weeks)												
1	randomised trials	serious [b]	not serious	not serious	not serious	none	847/908 (93.3%)	833/899 (92.7%)	**RR 1.01** (0.98 to 1.03)	**9 more per 1,000** (from 19 fewer to 28 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
ART adherence (follow up: 48 weeks; assessed with: self-reported (not missing any doses of drugs in last 4 weeks)												
1	randomised trials	serious [b]	not serious	not serious	not serious	none	829/908 (91.3%)	835/899 (92.9%)	**RR 0.98** (0.96 to 1.01)	**19 fewer per 1,000** (from 9 more to 37 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
CD4 cell gain (mean) at 24 weeks												
1	RCT	not serious	not serious	not serious	not serious	none	+113 cells/mm^3 , (95%CI 112.7-113.2)	+112 cells/mm ^{3}(95%CI 111.7-112.2)	**P = 0.85**		⊕⊕⊕⊕ HIGH	Limited importance

CI: Confidence interval; RR: Risk ratio; HR: Hazard Ratio. a. Imprecision: small numbers in sample size b. Self-reported, subjective outcome assessment. No blinding of participants or personnel

GRADE table: REMSTART trial

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cryptococcal antigen screening and early adherence support**	**standard care**	**Relative (95% CI)**	**Absolute (95% CI)**		
All-cause mortality at 12 months (follow up: 12 months)												
1	randomised trials	not serious	not serious	not serious	not serious	none	134/877 (15.3%)	180/843 (21.4%)	**RR 0.72** (0.57 to 0.90)	**60 fewer per 1,000** (from 21 fewer to 92 fewer) [b]	⊕⊕⊕⊕ HIGH	CRITICAL
Any new hospital admissions (follow up: 12 months)												
1	randomised trials	not serious	not serious	not serious	not serious	none	77/864 (8.9%)	73/836 (8.7%)	**RR 1.02** (0.74 to 1.41)	**2 more per 1,000** (from 23 fewer to 36 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Adherence to ART (follow up: 6 months; assessed with: Self -reported as not missing any pills in previous 28 days)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	421/467 (90.1%)	375/435 (86.2%)	**RR 1.05** (1.00 to 1.10)	**43 more per 1,000** (from 0 fewer to 86 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Adherence to ART (follow up: 12 months; assessed with: Self-reported as not missing any pills in previous 28 days)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cryptococcal antigen screening and early adherence support**	**standard care**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious [b]	not serious	not serious	not serious	none	451/509 (88.6%)	429/481 (89.2%)	**RR 0.99** (0.95 to 1.04)	**9 fewer per 1,000** (from 36 more to 45 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: Confidence interval; RR: Risk ratio

a, b Self-reported, subjective, no blinding out participants or personnel

Search Strategy

#1	HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "sexually transmitted diseases, viral"[MESH:NoExp]	354182
#2	randomization OR random [tw] OR double blind procedure OR single blind procedure OR clinical trial OR meta analysis OR meta-analy*[tw]	1327240
#3	severe immunodeficiency OR severe immuno-deficiency[tiab] OR severe immun*[tiab]	1504
#4	advanced disease [tiab] OR late presenters[tiab] OR late presentation [tiab] OR delayed diagnosis[tiab]OR delayed access to care[tiab]OR CD4 200[tiab] OR CD4 100[tiab]OR CD4 50[tiab]	23402
#5	#3 AND #4	24884
#6	#1 AND #2 AND #5	246

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