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Rapid initiation of antiretroviral therapy for people living with HIV (Review)

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[Intervention Review]

Rapid initiation of antiretroviral therapy for people living with HIV

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ABSTRACT

Background

Despite antiretroviral therapy (ART) being widely available, HIV continues to cause substantial illness and premature death in low-and-middle-income countries. High rates of loss to follow-up after HIV diagnosis can delay people starting ART. Starting ART within seven days of HIV diagnosis (rapid ART initiation) could reduce loss to follow-up, improve virological suppression rates, and reduce mortality.

Objectives

To assess the effects of interventions for rapid initiation of ART (defined as offering ART within seven days of HIV diagnosis) on treatment outcomes and mortality in people living with HIV. We also aimed to describe the characteristics of rapid ART interventions used in the included studies.

Search methods

We searched CENTRAL, the Cochrane Database of Systematic Reviews, MEDLINE, Embase, and four other databases up to 14 August 2018. There was no restriction on date, language, or publication status. We also searched ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform, and websites for unpublished literature, including conference abstracts.

Selection criteria

We included randomized controlled trials (RCTs) that compared rapid ART versus standard care in people living with HIV. Children, adults, and adolescents from any setting were eligible for inclusion.

Data collection and analysis

Two review authors independently assessed the eligibility of the studies identified in the search, assessed the risk of bias and extracted data. The primary outcomes were mortality and virological suppression at 12 months. We have presented all outcomes using risk ratios (RR), with 95% confidence intervals (CIs). Where appropriate, we pooled the results in meta-analysis. We assessed the certainty of the evidence using the GRADE approach.

Main results

We included seven studies with 18,011 participants in the review. All studies were carried out in low- and middle-income countries in adults aged 18 years old or older. Only one study included pregnant women.

In all the studies, the rapid ART intervention was offered as part of a package that included several cointerventions targeting individuals, health workers and health system processes delivered alongside rapid ART that aimed to facilitate uptake and adherence to ART.

Comparing rapid ART with standard initiation probably results in greater viral suppression at 12 months (RR 1.18, 95% CI 1.10 to 1.27; 2719 participants, 4 studies; moderate-certainty evidence) and better ART uptake at 12 months (RR 1.09, 95% CI 1.06 to 1.12; 3713 participants, 4 studies; moderate-certainty evidence), and may improve retention in care at 12 months (RR 1.22, 95% CI 1.11 to 1.35; 5001 participants, 6 studies; low-certainty evidence). Rapid ART initiation was associated with a lower mortality estimate, however the CIs included no effect when compared to standard of care (RR 0.72, 95% CI 0.51 to 1.01; 5451 participants, 7 studies; very low-certainty evidence). It is uncertain whether rapid ART has an effect on modification of ART treatment regimens as data are lacking (RR 7.89, 95% CI 0.76 to 81.74; 977 participants, 2 studies; very low-certainty evidence). There was insufficient evidence to draw conclusions on the occurrence of adverse events.

Authors' conclusions

RCTs that include initiation of ART within one week of diagnosis appear to improve outcomes across the HIV treatment cascade in low- and middle-income settings. The studies demonstrating these effects delivered rapid ART combined with several setting-specific cointerventions. This highlights the need for pragmatic research to identify feasible packages that assure the effects seen in the trials when delivered through complex health systems.

PLAIN LANGUAGE SUMMARY

Effects of starting antiretroviral therapy within one week of diagnosis on people living with HIV

What is the aim of this review?

The aim was to determine whether starting antiretroviral therapy (ART) within one week of HIV diagnosis (rapid ART) resulted in a lower risk of dying or better suppression of the virus in people's blood than standard care; as well as studying the effect of this intervention on whether people start taking ART and continue to be engaged in care after 12 months.

Key messages

Offering ART to people living with HIV (PLWH) within one week of diagnosis probably increases the number of people initiating the therapy at 12 months and the number of PLWH whose virus has been suppressed in the blood at 12 months. It may also improve the number of people who are still in contact with healthcare services at 12 months. We don't know the effect this has on people dying. We found that several other changes need to be made alongside rapid ART for services to achieve these outcomes.

What was studied in the review?

HIV is a leading cause of death worldwide. Although more people are taking ART than ever before, there is a large percentage of PLWH who are not being treated. One of the reasons identified is the long period between being diagnosed with HIV and starting ART. Rapid ART has been proposed as a way to increase the number of PLWH being started on ART and improve HIV-related outcomes.

What are the main results of the review?

We found seven studies that met the inclusion criteria of the review and assessed the effect of rapid ART on PLWH. Rapid ART probably increases the number of people being initiated on ART at 12 months and the number of PLWH with no detectable virus in their blood at 12 months (moderate-certainty evidence). Based on low-certainty evidence, rapid ART may increase the number of PLWH being retained in care. We don't know whether rapid ART has an effect on the number of deaths (very low-certainty evidence).

We found that if healthcare services aim to offer ART within a week of diagnosis, changes to how these systems operate will need to be made.

How up to date is the review?

We searched for relevant trials up to 14 August 2018.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Rapid ART compared to standard care for people living with HIV

Patient or population: people living with HIV
Setting: any
Intervention: rapid ART
Comparison: standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care	Risk with rapid ART				
Mortality at 12 months	44 per 1000	32 per 1000 (22 to 44)	RR 0.72 (0.51 to 1.01)	5451 (7 RCTs)	⊕◯◯◯ **Very low**[a,b,c]	We do not know if rapid ART has an effect on mortality after one year of follow-up
Virological suppression at 12 months	506 per 1000	597 per 1000 (556 to 642)	RR 1.18 (1.10 to 1.27)	2719 (4 RCTs)[d]	⊕⊕⊕◯ **Moderate**[e,f,g,h]	Rapid ART probably increases the likelihood of individuals being virally suppressed after 12 months
Retention in care at 12 months	538 per 1000	656 per 1000 (597 to 726)	RR 1.22 (1.11 to 1.35)	5001 (6 RCTs)	⊕⊕◯◯ **Low**[g,h,i,j]	Rapid ART may improve retention in care at 12 months.
Uptake of ART at 90 days	719 per 1000	942 per 1000 (848 to 1000)	RR 1.31 (1.18 to 1.45)	11,404 (4 RCTs)	⊕⊕◯◯ **Low**[h,k,l]	Rapid ART may improve uptake of ART at 90 days.
Uptake of ART at 12 months	870 per 1000	948 per 1000 (922 to 975)	RR 1.09 (1.06 to 1.12)	3713 (4 RCTs)	⊕⊕⊕◯ **Moderate**[h,k]	Rapid ART probably improves uptake of ART at 12 months.

Treatment modification	2 per 1000	23 per 1000 (4 to 119)	RR 7.89 (0.76 to 81.74)	977 (2 RCTs)	⊕◯◯◯ **Very low**[m,n]	We do not know the effect of rapid ART on treatment modification

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
Abbreviations: ART: antiretroviral therapy; CI: confidence interval; RR: risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Downgraded by one for risk of bias. All studies at high risk of bias due to large degree of attrition. As such the effect seen at population level is less clear.

[b] Downgraded by one for indirectness and qualitative heterogeneity. The largest studies, Elul 2017 and McNairy 2017, included individuals who were not eligible for antiretroviral therapy (ART) in denominators. The time of ART initiation varied across studies, with studies offering ART on the same day as diagnosis, within seven days or within 14 days. Cointerventions also varied significantly between studies.

[c] Downgraded by one for imprecision. Broad CIs containing clinically significant benefit and no effect.

[d] One study (McNairy 2017), measured virological suppression at 12 months only in those participants who received ART for at least six months. We did not, therefore, include this study in the pooled estimate of effect.

[e] Not downgraded for risk of bias. Although all studies had a large degree of attrition, we assumed that participants lost to follow-up were not receiving ART and, therefore, were not not virologically suppressed.

[f] Not downgraded for imprecision. Significant heterogeneity within the forest plot explained as McNairy 2017 calculated viral suppression in a subpopulation of participants on ART for six months.

[g] Downgraded by one for indirectness. Cointerventions delivered alongside rapid ART were different across studies. These cointerventions would affect the outcome measured.

[h] Not downgraded for imprecision. Given that rapid ART is a population-level intervention, we judge small increases in the likelihood of uptake of ART to be clinically significant.

[i] Downgraded by one for risk of bias. All the studies were unblinded. Participants were aware of receiving a different standard care, which could have made them more likely to be retained in care in the intervention arm.

[j] Not downgraded for inconsistency. There is moderate heterogeneity in the forest plot (I^2 = 54%). However, this did not reduce our certainty in the estimate of effect.

[k] Downgraded by one for risk of bias. All the studies were unblinded. The fact that participants and healthcare staff knew the allocation group could have influenced their performance, making them more likely to initiate ART.

[l]Downgraded by one for inconsistency. There is high heterogeneity between studies. Although this is partly explained by the different designs (for example, Koenig 2017 and Rosen 2016 offered ART on same day of diagnosis/enrolment, whilst Amanyire 2016 aimed to offer it within 14 days of diagnoses), heterogeneity remains high when similar studies are grouped together.

[m]Downgraded by two for imprecision. Few events and broad CIs for absolute risk containing no clinically appreciable effects and harm.

[n]Downgraded by one for qualitative and some statistical heterogeneity. One study shows increased treatment modification and the second shows no difference.

BACKGROUND

Description of the condition

At the end of 2017, there were approximately 36.9 million people living with HIV (PLWH) worldwide, most of them in low- and middle-income countries (LMICs) (WHO 2017). Although expansion of antiretroviral therapy (ART) over the last decade has halved HIV-related mortality (UNAIDS 2018), substantial challenges remain. In 2017, only 59% of PLWH were receiving ART (UNAIDS 2018), with high attrition from HIV services after HIV diagnosis (Govindasamy 2014; Losina 2010; Rosen 2011). This is particularly relevant in sub-Saharan Africa, where it is estimated that only 57% of those diagnosed with HIV are linked to care (Kranzer 2012). Many affected individuals who disengage from services during this period return only when they have deteriorated clinically and immunologically; resulting in high morbidity and mortality after ART initiation (Fairall 2008; Grinsztejn 2014; HMC 2015). Studies conducted in Ethiopia and sub-Saharan Africa estimate that PLWH may wait over a month to start ART, once eligibility is established (Bassett 2010; Lawn 2006; Reddy 2016; Teklu 2017). The reasons for these delays are complex and involve a combination of structural, social, and psychological patient factors (Hoehn 2017; Wachira 2014), as well as poor healthcare infrastructure in some settings (Govindasamy 2012).

One proposed intervention for improving linkage and retention of PLWH in HIV care is rapid ART initiation (starting ART as soon as possible after testing HIV-positive, normally within seven days) (Chan 2016; Pilcher 2017). PLWH previously attended HIV services several times for counselling and medical evaluation before starting treatment. Expediting ART initiation could potentially lead to earlier viral suppression in the medium- and long-term through improved uptake and adherence to ART as well as through improved retention in care (Hoenigl 2016; Pilcher 2017; Wilkinson 2015); what could result in lower overall mortality. Recent guidelines now advocate for ART initiation within seven days of HIV diagnosis (WHO 2018), with same-day initiation for those patients who feel ready, but ART initiation should be deferred if tuberculosis or cryptococcal meningitis is suspected or confirmed, to avoid paradoxical worsening of the existing infection which can be fatal (Ford 2018; WHO 2018).

There remains, however, uncertainty about the long-term treatment outcomes of rapid ART initiation (Mbonye 2016). Some concerns include insufficient adherence counselling/education; limited time to prepare psychologically for life with HIV and ART (Black 2014; Kim 2016), pill burden due to other concurrent co morbidities or conditions requiring urgent treatment (for example, tuberculosis) (Nachega 2014); and immune reconstitution inflammatory syndrome (IRIS), especially in individuals with advanced disease (CD4 counts < 200 cells/mm^3) (Uthman 2015), all of which could impact on morbidity and engagement in care (Hakim 2017). In addition, it is unclear what cointerventions facilitate long-term retention when rapid ART is provided within a package of care during widespread implementation of this treatment strategy.

In order to evaluate uptake, efficacy, safety, and to characterize rapid ART interventions compared with delayed or routine ART initiation we sought to consolidate findings from randomized controlled trials (RCTs) evaluating the intervention.

Description of the intervention

The current standard care post-HIV diagnosis varies across settings according to the local context (MacCarthy 2015). Countries often include in their national guidelines structural and individual interventions aimed to improve linkage. These include: integration of services, point-of-care CD4 cell count, post-test counselling, peer support, support with HIV disclosure, addressing any psychosocial barriers identified and others (NASCOP 2016; NCASC 2009; NDOHSA 2015; Wynberg 2014). Pre-ART care routinely involves a baseline clinical and a psychosocial assessment (MoH 2016) including; physical examination, laboratory tests, opportunistic infection screening, nutritional status assessment, counselling, health insurance evaluation, and education sessions (NDOHSA 2015; Pilcher 2017). These assessments were previously carried out over several visits to HIV services, resulting in delays in ART initiation, often for several weeks, after PLWH were considered eligible for ART (Lawn 2006; Teklu 2017).

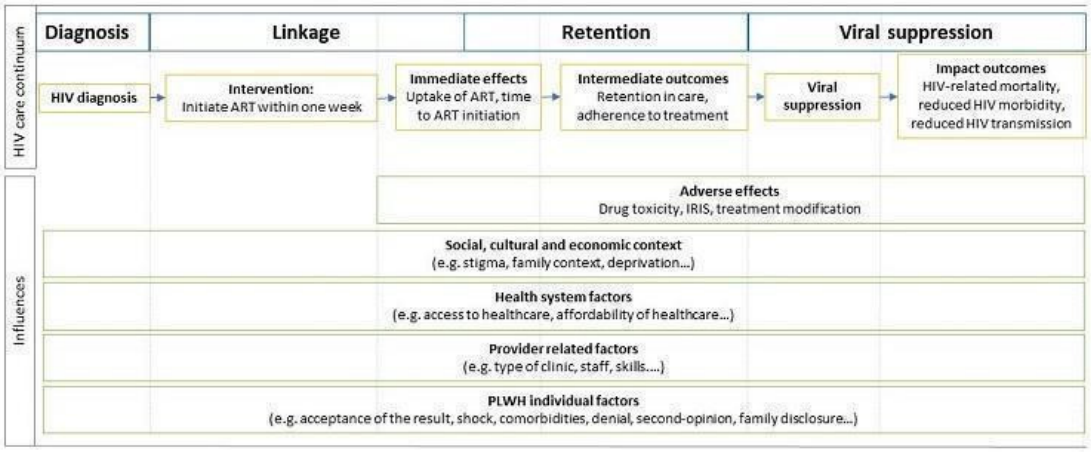
For the purposes of this Cochrane Review, we define rapid ART as offering the therapy within seven days after eligibility for ART. According to current guidelines, PLWH are considered eligible for ART on the same day as diagnosis unless they are found to have signs or symptoms of opportunistic infections such as tuberculosis or cryptococcal meningitis. With rapid ART, PLWH may receive usual care, but some of the interventions that form part of pre-ART care are delivered on the same day or within a few days of HIV diagnosis. These include, among others, screening for tuberculosis, physical examination and an initial counselling and education session (Labhardt 2016; Pilcher 2017; Rosen 2016).

How the intervention might work

Delaying the initiation of ART has been identified in the literature as a major contributor to disengagement, particularly in LMICs (Govindasamy 2014), and rapid ART has the potential to improve linkage and retention in HIV care on several levels; the simplification and reduction in number of unnecessary clinic visits could help PLWH to overcome financial and logistic barriers in access to care and, consequently, reduce loss to follow-up during the pre-ART period (Pilcher 2017; Rosen 2016). Lower loss to follow-up may increase the absolute number of PLWH achieving viral suppression (Pilcher 2017; Rosen 2016), reduce HIV transmission, and HIV-related morbidity, and mortality (Eshleman 2017; Lesko

2016; Mfinanga 2015). The HIV continuum of care is however a complex process, in which every cascade step is influenced by multiple factors, as illustrated in our conceptual model (Figure 1). The feasibility and acceptability of rapid ART initiation depends on various health system and provider factors, such as: staffing levels, skills, infrastructure and equipment, which vary across settings (Attawell 2003); as well as: social; economic; cultural; and individual drivers, including acceptance and motivation to take ART (Black 2013; Black 2014; Katirayi 2016). Initiating treatment before baseline screening test results are available could also result in a higher frequency of adverse events which may result in disengagement (Abay 2015; Chan 2016; Pilcher 2017), and regimen modification (Pilcher 2017). It is essential that some these negative influencing factors are limited for rapid ART initiation to result in successful linkage and long-term retention in care.

Figure 1. Conceptual model of factors influencing the HIV care continuum
ART: antiretroviral therapy, IRIS: immune reconstitution inflammatory syndrome; PLWH: people living with HIV



Why it is important to do this review

With universal ART being adopted worldwide, interventions aimed at improving linkage to care - such as rapid ART - are increasingly relevant. But, despite evidence that rapid ART improves linkage and short term retention in care (Ford 2018; Rosen 2016), there remains uncertainty regarding long-term outcomes, particularly for those who start ART on the same-day of diagnosis. In addition, evidence of improved uptake and retention has, in part, been based on studies where the research context may have substantially influenced outcomes (Geng 2017). Given these concerns, we undertook a systematic review which rigorously appraises and synthesizes evidence from RCTs of rapid ART and characterizes the components of study interventions, in order to further clarify the role of rapid ART initiation in HIV care.

OBJECTIVES

To assess the effects of rapid initiation of ART (defined as offering ART within seven days of HIV diagnosis) on treatment outcomes

and mortality in people living with HIV (PLWH). We also aim to describe the characteristics of rapid ART interventions used in the included studies.

METHODS

Criteria for considering studies for this review

Types of studies

We included all RCTs in which the unit of randomization was either the individual or a cluster. We did not include non-randomized studies as we anticipated there to be a significant evidence base from randomized studies. Additionally, any effect seen in non-randomized studies is likely to be confounded due to the nature of the intervention.

Types of participants

Inclusion criteria

- Adults (aged 19 years or older), adolescents (aged 10 to 18 years), and children (aged 1 to 9 years) with a positive HIV test (either a positive antibody test, a positive antigen test, or a positive nucleic acid test), who were known not to have previously received ART.
- Pregnant women who were receiving life-long ART for their own health (Option B+ of the WHO system, see Table 1; WHO 2012).

Exclusion criteria

- PLWH who receive ART in the context of pre-exposure prophylaxis or post-exposure prophylaxis, or both.
- Infants (aged 0 to under 1 year).
- Pregnant women not receiving life-long ART for their own health.

We excluded the last two groups (infants and pregnant women) because they may have received ART as part of prevention of mother to child transmission programmes, which did not include life-long ART. For example, under WHO's Options A and B-, pregnant women with high CD4 cell counts and infants received only a short course of antiretrovirals (WHO 2012).

Types of interventions

Experimental interventions

Any intervention that aims to initiate life-long ART within seven days of HIV diagnosis. This may be combined with several other services, including education, counselling, addressing social determinants, clinical and laboratory assessments, or treatment of comorbid conditions.

Comparator interventions

Comparison interventions offering the standard package of HIV care. We included studies that used the same CD4/clinical stage thresholds for ART initiation in both intervention and comparison groups.

Cointerventions

We included studies that offered rapid ART initiation within a package of care alongside other interventions. These complex interventions showed marked variation and we therefore describe these narratively, including a comparative table (Table 2).

Types of outcome measures

Primary outcomes

- All-cause mortality rate.
- Virological suppression 12 months after a positive HIV test.

According to the WHO, viral suppression refers to "a viral load below the detection threshold using viral assays" and defines viral failure as the inability to achieve a viral threshold below 1000 copies/mL (WHO 2016). However, there is inconsistency in the thresholds used in different settings and time periods to define viral suppression (AIDSinfo 2015; EACS 2017; NASCOP 2016; NDOHSA 2015). For this reason, we used the investigators' study definitions of virological suppression or undetectable viral load.

Secondary outcomes

- Retention in HIV care at 12 months after a positive HIV test. We defined retention according to WHO guidelines, as PLWH "who are enrolled in HIV care and routinely attend these services in accordance to their needs" (WHO 2016). This definition excludes those PLWH who either die or are lost to follow-up. We considered the follow-up period to start at the point of randomization to the intervention or comparator arm of any study. There is a lack of consensus on the period of time that a PLWH has to be disengaged with HIV services to be considered lost to follow-up, usually ranging from three to six months after the last attendance to services (Hønge 2013; Pilcher 2017). A systematic review that analysed the sensitivity and specificity of thresholds for loss to follow-up in 41 countries concluded that the most appropriate definition would be failure to engage with

services for more than 180 days after the last visit (Chi 2011). Due to the variability and lack of a standard definition, we used the investigators' study definitions of loss to follow-up.

- Uptake of ART, defined as the proportion of eligible PLWH offered ART who initiated the therapy.
- ART adherence, as documented by self-report, pill count, pharmacy refills, or real-time electronic monitors such as MEMScaps or Wisepill (Pellowski 2014), or a combination of any or all of these.
- Incidence of treatment modification, defined as the number and proportion of PLWH on ART who experience a regimen modification in the intervention and control groups.

Adverse outcomes

We analysed the number and proportion of PLWH experiencing adverse drug reactions associated with ART in the intervention and control groups and the number of HIV-negative people partnered with a HIV-positive person who became infected with HIV during the study in each group. We also analysed the incidence of IRIS, as defined by the study authors, and we included both paradoxical and unmasking IRIS (AIDSinfo 2017).

Search methods for identification of studies

Electronic searches

Databases

We searched the following databases for relevant studies using terms listed in Appendix 1;

- Central Register of Controlled Trials (CENTRAL 2018, Issue 8) in the Cochrane Library (15 August 2018).
- Cochrane Database of Systematic Reviews (CDSR) (15 August 2018).
- MEDLINE (PubMed) (1966 to 15 August 2018).
- Embase Ovid (1947 to 15 August 2018).
- African Index Medicus (AIM) (1990 to 15 August 2018).
- Latin American and Caribbean Health Sciences Literature (LILACS) (1982 to 15 August 2018).
- Web of Science-Core Collection (1970 to 15 August 2018).

We performed searches up to 15 August 2018. There was no restriction on date, language, or publication status.

International trials registries

We searched the following trials registries for unpublished or ongoing studies:

- ClinicalTrials.gov (www.clinicaltrials.gov) (15 August 2018).
- WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch/) (15 August 2018).

Searching other resources

Grey literature

We searched the following sources of grey literature to identify any relevant unpublished literature, including conference abstracts:

- International AIDS Society Online Resource Library (library.iasociety.org/GlobalSearch.aspx).
- websites of the International AIDS Conference (IAS) on HIV Science, International AIDS Conference, International Conference on AIDS and STIs in Africa (ICASA), and the Conference on Retroviruses and Opportunistic Infections (CROI) for the years 2013, 2014, 2015, 2016, 2017, and 2018.
- the RAND publication database (www.rand.org/search.html).

Reference lists

We handsearched the reference lists of all included studies and relevant systematic reviews to identify additional studies (for example, unpublished or in-press citations).

Correspondence

We contacted study authors and subject experts for information on unpublished or ongoing studies, or to request additional study data where we considered necessary.

Data collection and analysis

Selection of studies

We merged studies identified by the keyword searches of different databases and removed duplicate reports. Two review authors independently evaluated all the studies by reading the abstracts to identify potentially relevant studies. We obtained full-text copies of those articles that were potentially eligible and we decided on whether the studies met the inclusion criteria with the aid of a study eligibility form (see Appendix 2). We resolved all disagreements by consulting a third review author. We listed all studies excluded after full-text assessment in the Characteristics of excluded studies table.

Data extraction and management

Two review authors independently extracted data from included studies using a pre-piloted data collection tool. We resolved any discrepancies by discussion, consulting a third review author when necessary. Data points for extraction included the following:

- methods: study aim, design, unit of allocation, method of allocation, and duration of study. For cluster-RCTs we extracted the unit of analysis, the method of analysis, the average cluster size, and the intraclass correlation coefficient (ICC);
- participants: setting, number, inclusion/exclusion criteria, participant's sociodemographic characteristics, method of recruitment, withdrawals, and losses to follow-up;
- intervention and control: number of participants/clusters randomized to intervention and control, description of intervention and control, including time of ART initiation, eligibility criteria, and complexity of intervention;
- outcomes: definition of outcome, method of measurement, time points measured, person measuring, unit of measurement, statistical power, and imputation of missing data;
- other: ethical approval, information consent, source of funding, and possible conflicts of interests.

Assessment of risk of bias in included studies

Two review authors examined the components of each included study for risk of bias using the Cochrane 'Risk of bias' tool (Higgins 2017). This includes detailed information on sequence generation, allocation concealment, blinding (participants, personnel, and outcome assessor), incomplete outcome data, selective outcome reporting, and other sources of bias (Higgins 2017). For cluster-RCTs included in the review, we also assessed the risk of bias by including the five additional criteria specified in Section 16.3.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed the methodological components of the studies and have classified these as adequate (low risk of bias), inadequate (high risk of bias), or unclear, as explained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We also assessed and report the likely magnitude and direction of biases and their likely impact on the findings. We resolved any discrepancies by discussion or by consulting a third review author.

Measures of treatment effect

Dichotomous data

We reported outcome measures for dichotomous data (for example, viral suppression yes/no) as risk ratios (RR) with 95% confidence intervals (CIs).

Continuous data

Studies did not report continuous data for the outcomes of interest in this review.

Timing of outcome assessment

For the outcomes of virological suppression and retention in care at 12 months, we accepted the result closest to 12 months within the range of 5 to 14 months. This is slightly different from the 6 to 14-month range specified in the protocol. See Differences between protocol and review for the rationale of extending the range.

For the secondary outcomes of incidence of treatment modification and of number of people experiencing adverse drug events we accepted the result closest to 12 months within a range of 6 to 14 months.

Unit of analysis issues

Cluster-RCTs

For cluster-RCTs, we used adjusted effect estimates and standard errors in our meta-analysis using the generic inverse-variance method in Review Manager 5 (RevMan 5; Review Manager 2014). When studies did not perform any adjustment for clustering, we adjusted the raw data ourselves using the intraclass correlation coefficient (ICC).

Repeated observations on participants

Some studies reported results from more than one time point. In those cases we conducted separate analyses according to the different outcomes defined (see Primary outcomes; Secondary outcomes).

Studies with multiple treatment groups

One study (Elul 2017), included two different experimental arms (combination intervention strategy (CIS) and CIS+ where participants also received non-cash financial incentives) and a single control arm. (See Characteristics of included studies.) In order to avoid double counting in the meta analysis we included the estimate of effect from the CIS versus control comparison only. We were unable to split the control arm as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017), as the study authors had adjusted for clustering using random-intercept log-Poisson regression. We could have cluster-adjusted the data ourselves, however, this would have produced a less precise estimate of effect. As there was no significant difference between the CIS arm and the CIS+ arm for any of the outcomes included in the review we decided to present the effect estimate from the CIS arm versus control comparison only.

Dealing with missing data

We attempted to contact the study authors to obtain missing data when the lack of reporting of necessary data restricted the use of the study.

We applied no imputation measures for missing data.

In order to analyse data as intention-to-treat we kept participants in the group to which they had been randomized, regardless of whether they had actually received the intervention (rapid ART) or not. Furthermore, to calculate primary and secondary outcomes, we included in the denominator all randomized participants (Higgins 2011).

Assessment of heterogeneity

We assessed the statistical heterogeneity in each meta-analysis by inspecting forest plots and calculating Chi^2 test values (Deeks 2017), and I^2 statistics (Higgins 2003). We considered significant heterogeneity to be present if the P value of the Chi^2 test was less than 0.10. We interpreted the I^2 statistic according to the thresholds recommended in the *Cochrane Handbook of Systematic Reviews of Interventions* (Deeks 2017):

- 0% to 40%: low heterogeneity;
- 30% to 60%: moderate heterogeneity;
- 50% to 90%: substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

We explored the causes of statistical heterogeneity by conducting a subgroup analysis (see Subgroup analysis and investigation of heterogeneity). We also explored clinical and methodological heterogeneity by assessing study populations, methods used, and interventions delivered.

Assessment of reporting biases

We intended to use funnel plot analysis and statistical tests (such as the Egger regression test) to assess for publication bias. We planned to perform funnel plot analysis if there were more than 10 studies in any meta-analysis. As there were fewer than 10 studies included in any of the effects analyses, we did not perform an assessment of reporting biases (Sterne 2017).

Data synthesis

We analysed data using RevMan 5 (Review Manager 2014). We performed meta-analysis where appropriate, using a fixed-effect model where we found no or low heterogeneity, according to thresholds designated above. For outcomes where we found moderate or substantial heterogeneity we used a random-effects model in our analysis. We expressed the results of the primary outcomes using forest plots. We also used forest plots to express the results of the following secondary outcomes: retention in care at 12 months, uptake of ART at 90 days and 12 months; and incidence of treatment modification (Deeks 2017). Study authors did not report data on the secondary outcomes of ART adherence and incidence of IRIS. We, therefore, we did not include these outcomes in our analysis. For cluster-RCTs, we used adjusted effect estimates if reported. When adjusted effect estimates were not reported, we adjusted the raw data using the reported ICC (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

We planned to carry out subgroup analyses by CD4 count (200 cells/μL or more, or fewer than 200 cells/μL), time to ART initiation, age group, and geographical location, to investigate potential sources of heterogeneity. We, however, did not find enough data to carry out subgroup analysis by severity of HIV infection, as only one study (Koenig 2017), stratified the results according to our pre-specified CD4 count threshold (200 cells/μL). We did not carry out a subgroup analysis by participants' age group or by geographical location because none of the included studies recruited children or adolescents, and because all the studies were carried out in LMICs.

Although we initially planned to only include studies where participants randomized to the rapid ART group were offered the therapy within seven days of diagnosis, we decided to include other studies in which ART was expedited and where most participants randomized to the intervention group were offered ART within the first days after diagnosis, even if researchers did not use the seven-day threshold to define the intervention. We clarified this difference in the Differences between protocol and review section and we carried out a subgroup analysis by time of ART initiation. Four studies aimed to offer ART on the same day as diagnosis/enrolment to the study, to PLWH randomized to the intervention arm (Koenig 2017; Labhardt 2018; Rosen 2016; Stevens 2017). One study aimed to offer ART to the intervention arm within seven days of enrolment (McNairy 2017). Elul 2017 aimed to offer ART within the first clinic visit in the intervention arm, which was expedited. Amanyire 2016 aimed to offer ART within 14 days of enrolment to those in the rapid ART group. Also, during the review process, we identified significant variation in study design. As such, we conducted a subgroup analysis according to study design (cluster-designed RCTs versus individual RCTs).

Sensitivity analysis

We planned to conduct sensitivity analyses to investigate the effect on the outcomes of:

- including and excluding studies we considered to be at high risk of bias for random sequence generation according to Cochrane's 'Risk of bias' assessment;
- analysing the different assumptions made when imputing missing data;
- analysing retention in care using different thresholds for loss to follow-up.

However, we did not find any study at high risk of bias for random sequence generation. All the studies used similar assumptions to input missing data. All studies used similar thresholds to define retention in care. We therefore did not carry out any of the planned sensitivity analyses.

'Summary of findings' table

We created a 'Summary of findings' table using GRADEpro software (GRADEpro 2015), which displays the primary and secondary outcomes of the review (see Types of outcome measures), the comparative risks between intervention and control groups, the relative effects with 95% CIs, the number of participants in the studies, and the certainty of the evidence. We classified the certainty of the evidence for each of the outcomes as high, moderate, low, or very low, according to an assessment using the five criteria (limitations, inconsistency, indirectness, imprecision, and publication bias) of the GRADE system (GRADE 2004).

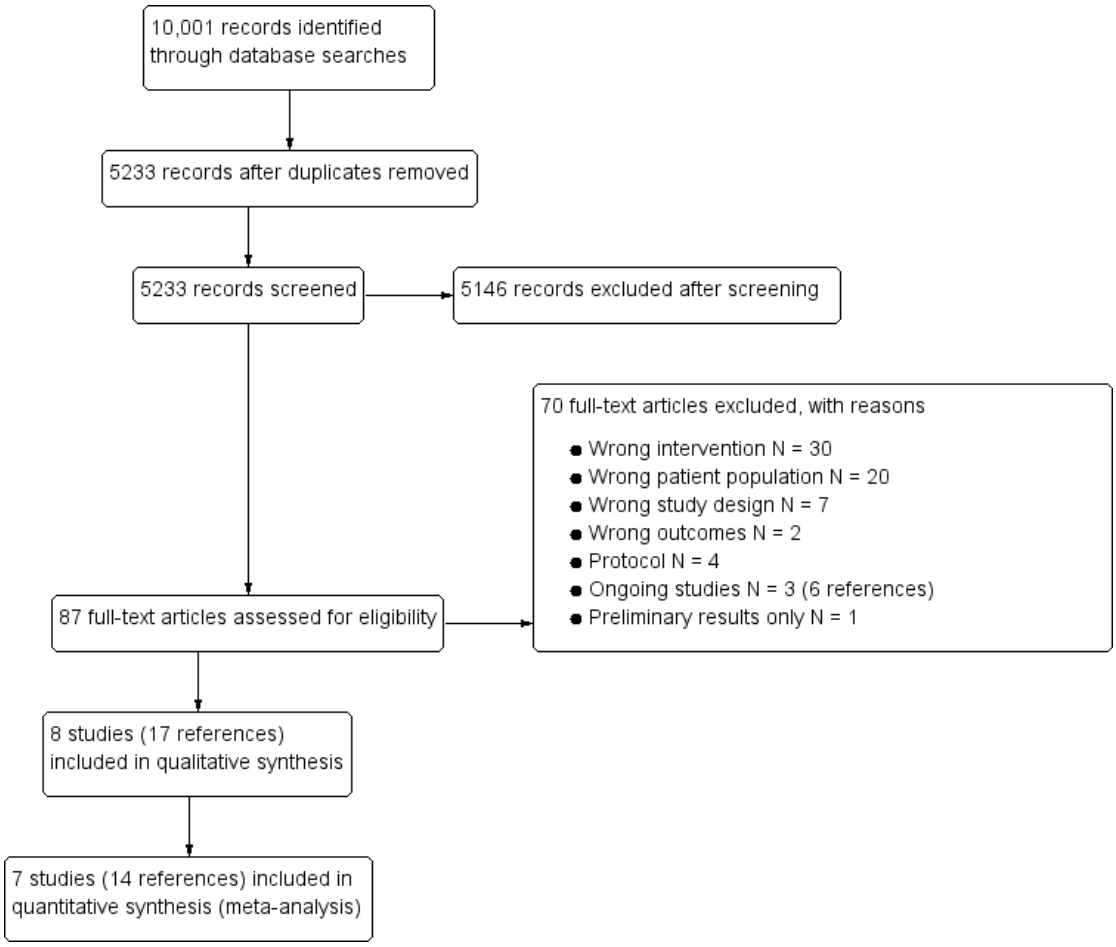
RESULTS

Description of studies

Results of the search

We identified 10,001 references from two searches: an initial search in February 2018 found 9313 references; and in August 2018 a further 688 references were found. From these, after removing duplicates, we identified 5367 unique references. We considered 5146 irrelevant to our review on initial screening. We considered 87 references for inclusion, of which we excluded 70, with reasons. Seventeen references from eight unique studies met our inclusion criteria and are included in the review. One of the studies was only included in the qualitative synthesis; this is an ongoing study where only preliminary results were available. We identified four ongoing studies that may meet our inclusion criteria. The search results and the reasons for exclusion are presented in a PRISMA flow diagram (see Figure 2; Moher 2009).

Figure 2. Study flow diagram



Included studies

See Characteristics of included studies, Table 2, and Table 3.

Study design

We included seven studies in our quantitative analysis. Three were cluster-RCTs (Amanyire 2016; Elul 2017; McNairy 2017). Three used individuals as the unit of randomization (Koenig 2017; Rosen 2016; Stevens 2017). One study used households as the unit of randomization (Labhardt 2018). This study randomized households with more than one eligible individual to the same group to reduce contamination. In total, they included 274 individuals from 264 households. The study authors reported that, as there were only 10 households including two participants, cluster-adjustment did not produce stable results and so they did not carry out this procedure. In our review we agreed with the study authors and analysed this study as an individual RCT.

Participants and setting

All the studies included participants aged 18 years or older. Only one study included pregnant women (Stevens 2017). Female participants constituted 48% to 66% of study populations and the median CD4 count at ART initiation was above 200 cells/μL for most but ranged from 165 to 417 cells/μL across study arms. CD4 threshold to determine eligibility of ART differed across studies. In Elul 2017, McNairy 2017, Rosen 2016, and Stevens 2017, participants were eligible for ART if their CD4 count was less than 350 cells/mm^3. Amanyire 2016 and Koenig 2017 started with the same threshold (350 cells/mm^3) but, following changes in national guidelines, changed the ART eligibility criteria during the study to include all participants with CD4 count fewer than 500

cells/mm^3. Labhardt 2018 was the only study to consider PLWH eligible for ART irrespective of their CD4 count. All were conducted in LMICs: two in South Africa; and one each in Lesotho, eSwatini (formerly known as Swaziland), Uganda, Mozambique, and Haiti. Two studies were conducted in urban settings (Koenig 2017; Rosen 2016), one in a rural setting (Labhardt 2018), three in a mixture of rural and urban healthcare facilities (Amanyire 2016; Elul 2017; McNairy 2017), and one did not specify location (Stevens 2017).

Interventions

Four studies aimed to start participants on ART on the same day as diagnosis (Koenig 2017; Labhardt 2018; Rosen 2016; Stevens 2017). Elul 2017 offered ART on the first clinic visit; McNairy 2017 aimed to offer ART within seven days of diagnosis and Amanyire 2016 within 14 days of diagnosis. We have summarized the main characteristics of the included studies in Table 3.

Most studies conducted some assessment of 'readiness to start ART' (Amanyire 2016; Koenig 2017; Labhardt 2018; Rosen 2016; McNairy 2017). In Labhardt 2018, PLWH were asked if they were ready to start ART. Amanyire 2016 changed the way they carried out adherence counselling sessions to a more individualized approach. Rosen 2016 assessed readiness to start ART during counselling sessions. McNairy 2017 used a checklist, and Koenig 2017 assessed readiness through a survey administered by a social worker.

Cointerventions

We found that rapid ART was frequently delivered alongside several other interventions (Amanyire 2016; Elul 2017; Koenig 2017; Labhardt 2018; McNairy 2017; Rosen 2016; Stevens 2017), targeted at modifying individual or health workers' behaviours, or at modifying health system processes (Table 2). At the individual level, two studies included short message service (SMS) visit reminders or noncash financial incentives, or both (Elul 2017; Koenig 2017; McNairy 2017). Other studies expedited drug dispensing at the pharmacy for those randomized to the rapid ART arm (Rosen 2016), or included additional information highlighting the importance of adherence to treatment (Labhardt 2018). At the health-system level; the number of pre-ART counselling sessions was reduced and they were frequently delivered on the day of HIV diagnosis (Elul 2017; Koenig 2017; Labhardt 2018; McNairy 2017; Rosen 2016; Stevens 2017). Five studies introduced measures to obtain real-time point-of-care (POC) CD4 results in the rapid ART arm (Amanyire 2016; Elul 2017; McNairy 2017; Rosen 2016; Stevens 2017). One study also described expediting tuberculosis (TB) screening before they offered ART (Rosen 2016). In Amanyire 2016, Rosen 2016, and Stevens 2017, healthcare workers received training on the new procedures and instruments implemented (for example, POC instruments) before rapid ART was delivered.

Table 2 summarizes cointerventions delivered alongside rapid ART in the included studies.

Outcomes

All seven studies reported on mortality and uptake of ART. Five studies reported virological suppression at 12 months, with only Elul 2017 and Stevens 2017 not reporting on this outcome. One study, Amanyire 2016, reported mortality and viral suppression for a randomly selected subset of study participants; these were then inverse-probability weighted to represent the total study population and determine effect estimates.

All the included studies reported retention in care, using different definitions to classify participants as lost to follow-up and to measure retention in care. Elul 2017 and McNairy 2017 classified participants as retained in care if they attended a clinic visit within the 90 days prior to the end of the study (12 months after randomization). Koenig 2017 defined retention in care as attending the 12-month visit (1 clinic visit between 12 and 15 months after HIV testing). Rosen 2016 classified participants as retained in care if they attended a clinic visit within 5 to 10 months after study enrolment. Labhardt 2018 classified participants as retained in care if either they or a treatment "buddy" attended a health facility to get a drug refill between 11 and 14 months after enrolment. Stevens 2017 defined retention in care as participants not missing an appointment by over 60 days; and reported the results at 6 and 12 months. We used the 12-month data in our analysis because it was closer to the other studies' measuring time. We could not use data from Amanyire 2016 in the retention analysis as they measured the mean number of visits per 90 days in each group.

We found two studies that reported on treatment modification (Koenig 2017; Labhardt 2018).

Excluded studies

See Characteristics of excluded studies.

We excluded several studies as they assessed the effect of ART initiation related to CD4 threshold rather than initiating ART soon after HIV diagnosis (Achhra 2017; Danel 2015; Iwuji 2017; Sabapathy 2017; Larmarange 2016; Plazy 2016; Temprano 2015). We further excluded studies that specifically assessed timing of ART in participants who had oppurtunistic infections such as cryptococcal meningitis or tuberculosis meningitis (Bisson 2013; Blanc 2011; Boulware 2014; Degu 2012; Grant 2010; Havlir 2011; Laurelliard 2013; Makadzange 2010). We considered that these studies focused on population subgroups, whose clinical management and guidelines differ from those of the general population of PLWH (WHO 2018).

Studies awaiting classification

We did not identify any studies awaiting classification.

Ongoing studies

We identified three ongoing studies (Rosen 2017; PACTR201706002322546a; Sikazwe 2018). For more details about ongoing studies see the Characteristics of ongoing studies section.

Risk of bias in included studies

See Figure 3 and Figure 4 for a summary of the 'Risk of bias' assessments. We have presented further details in the Characteristics of included studies section.

Figure 3. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies

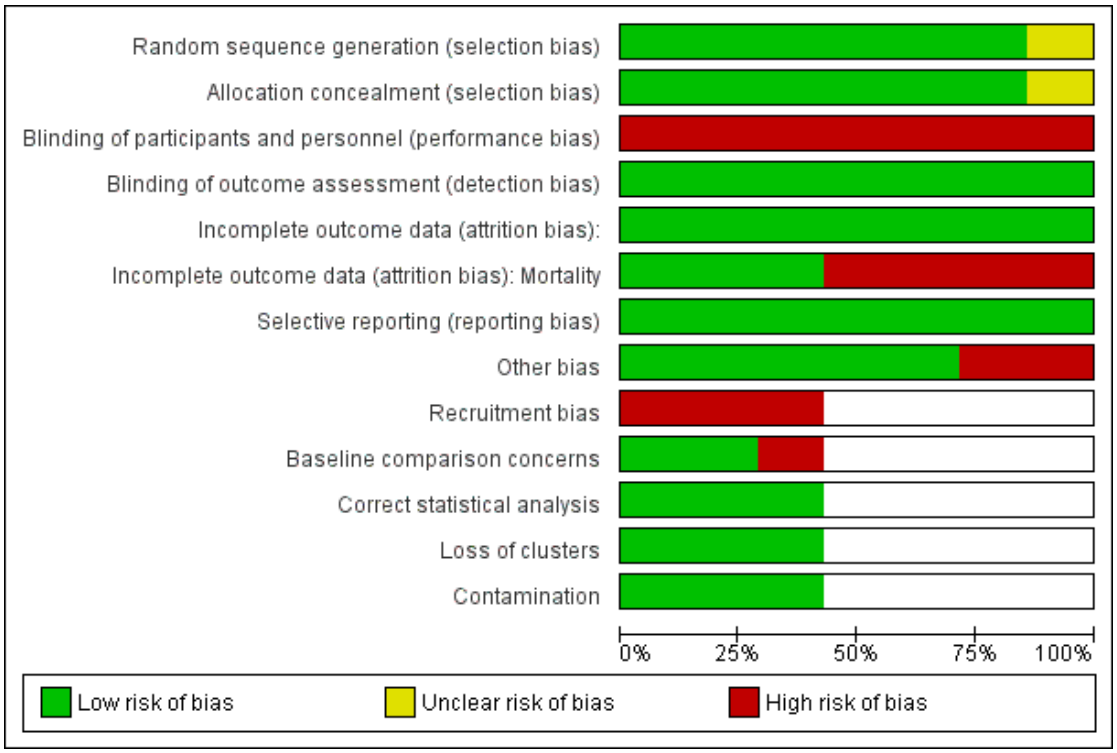
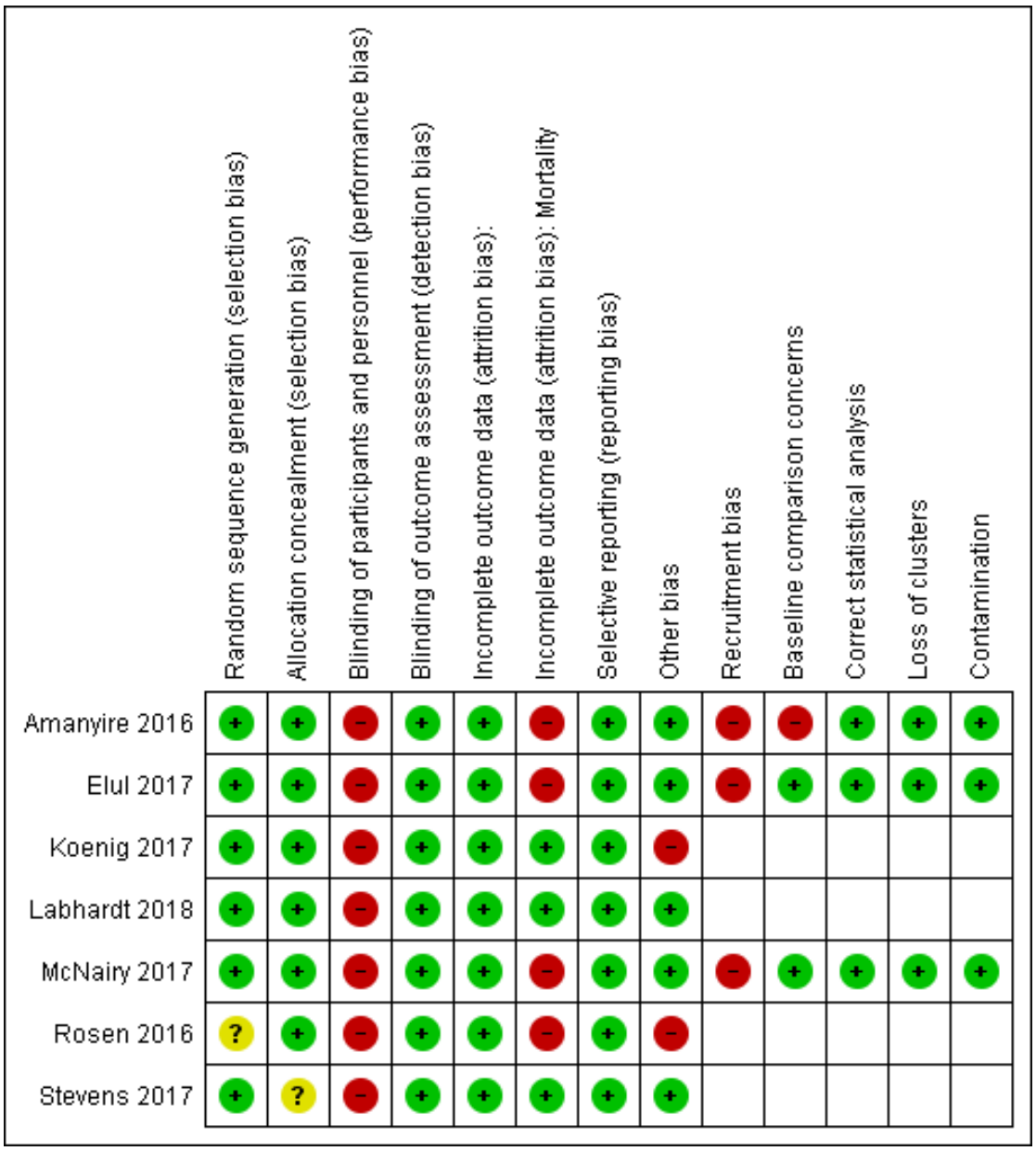


Figure 4. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study



Allocation

Sequence generation

Six studies described the use of random methods in the sequence generation process, so we judged them to be at low risk of bias for this domain. One study, Rosen 2016, did not explain in detail the methods used to create the sequence generation. For this reason we judged this study to be at unclear risk of selection bias.

Allocation concealment

Six studies described the use of appropriate allocation concealment methods, such as opaque envelopes, which prevented participants and investigators from foreseeing the allocation group of participants, so we judged them to be at low risk of selection bias. One study, Stevens 2017, did not describe allocation concealment methods; we therefore judged it as unclear risk of bias in this domain.

Blinding

Performance bias

We judged all seven studies to be at high risk of performance bias. All studies were open-label studies and could not mask participants or personnel. Whilst we acknowledge that the nature of the intervention made blinding impossible, we judged that lack of blinding could affect the performance of participants. Participants could be more likely to be retained in care and be initiated on ART if they were aware that they were part of the experimental arm of a study. Personnel could also be more likely to encourage participants to remain in care or to initiate ART, or both, if they were aware of which participants were in the intervention group. This could have an effect not only on the outcomes of retention in care and ART uptake, but also on the primary outcomes, as individuals who initiate ART and are retained in care are more likely to be virologically suppressed.

Detection bias

Three studies collected data on the outcomes through retrospective medical records (Elul 2017; McNairy 2017; Rosen 2016). Three studies gave no information about blinding of outcome assessors (Amanyire 2016; Labhardt 2018; Stevens 2017), and one study reported that statisticians were not blinded (Koenig 2017).
We judged all studies to be at low risk of detection bias, as the outcomes measured were objective and did not rely on interpretation or on self-reported measures.

Incomplete outcome data

We judged separately attrition bias for the outcome of mortality because we considered that ascertaining this outcome in PLWH lost to follow-up was more problematic than for the outcomes of virological suppression, retention in care, or uptake of ART; as we deemed reasonable to consider those lost to follow-up as not being virologically suppressed, initiated ART or retained in care, as most authors did. We judged four studies to be at high risk of attrition bias for the outcome of mortality because attrition rates were high and significantly different between the intervention and the control groups (Amanyire 2016; Elul 2017; McNairy 2017; Rosen 2016). They ranged from 19% to 42% in the intervention group and from 21% to 56% in the control group. We judged Koenig 2017 and Labhardt 2018 to be at low risk of attrition bias for the outcome of mortality because attrition rates were below 25% in both groups. Stevens 2017 had high rates of attrition in both arms. We judged it to be at low risk of bias for the outcome of mortality because they undertook additional efforts to ascertain vital status. The mortality rate found was in-line with that described in other cohorts.
We did not consider that high attrition rates would bias the estimate effect of virological suppression, as we judged it appropriate to assume that PLWH lost to follow-up would not be virologically suppressed. We judged that attrition would not affect the outcomes of retention in care and uptake of ART for the same reason. So, we judged all studies to be at low risk of attrition bias for these outcomes.

Selective reporting

We judged all the studies to be at low risk of reporting bias. Six studies prespecified the outcomes measured in published protocols. We did not find prespecified outcomes for Stevens 2017, but they reported all relevant and non-significant outcomes.

Other potential sources of bias

We judged two studies to be at high risk of bias in the selection of participants because these studies enrolled only those participants who were ready to commence ART (Koenig 2017; Rosen 2016). This could potentially bias the estimates of effect for the outcomes of uptake and retention in care by introducing bias in the selection of participants. The other studies did not exclude participants on the basis of being ready to start ART (Amanyire 2016; Elul 2017; Labhardt 2018; McNairy 2017; Stevens 2017).

Risk of bias in cluster-RCTs

We assessed five additional risks of bias in the three cluster-RCTs, as recommended by the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011): recruitment bias, baseline comparison concerns, missing clusters, correct statistical analysis, and contamination.

Recruitment bias

We judged all three studies to be at high risk of recruitment bias (Amanyire 2016; Elul 2017; McNairy 2017). Participants were aware of the clinics allocated to the intervention group, which could have made them more likely to seek care at these clinics due to the perception of receiving higher quality of care.

Baseline comparison concerns

We found no baseline imbalances in two studies (Elul 2017; McNairy 2017). One study had significant imbalances between the intervention and control group at baseline and we judged it to be at high risk of bias for this domain (Amanyire 2016).

Loss of clusters

None of the trials lost any cluster to follow-up and they included all randomised clusters in the analysis, so we judged all studies to be at low risk of bias for this domain

Statistical analysis

All studies described appropriate statistical methods of adjusting for clustering and we judged them to be at low risk of bias in this domain.

Contamination

Given the nature of the intervention and the outcomes analysed, we considered that a "herd effect" leading to contamination was unlikely and, therefore, we judged them to be at low risk for this domain.

Effects of interventions

See: **Summary of findings for the main comparison** Rapid antiretroviral therapy (ART) compared to standard care for people living with HIV

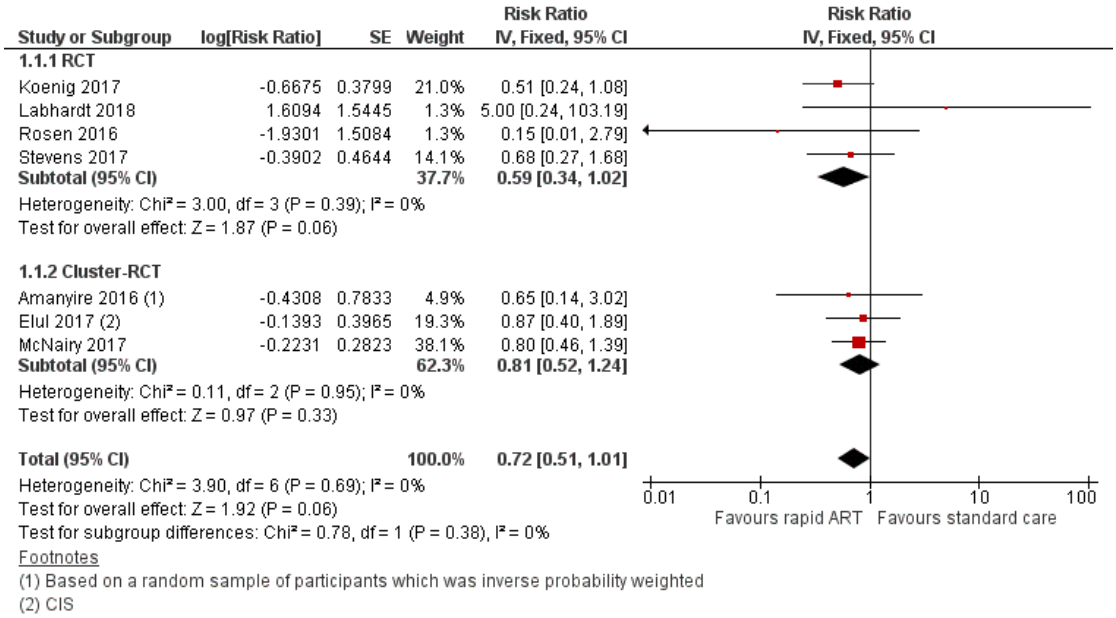
We have presented main effects and subgroup analyses. Subgroup analyses should be interpreted with caution due to the limited number of studies contributing to subgroups for all analyses. We have also presented main effects and GRADE assessments in Summary of findings for the main comparison

Primary outcomes

Mortality

There was some evidence that rapid initiation of ART in people newly diagnosed with HIV reduced the risk of dying. However, this effect was not seen at the 95% confidence level (RR 0.72, 95% CI 0.51 to 1.01; 5451 participants, 7 studies; I^2 = 0%; very low-certainty evidence; Analysis 1.1; Figure 5).

Figure 5. Forest plot of comparison 1. Rapid ART versus standard care, outcome 1.1, mortality

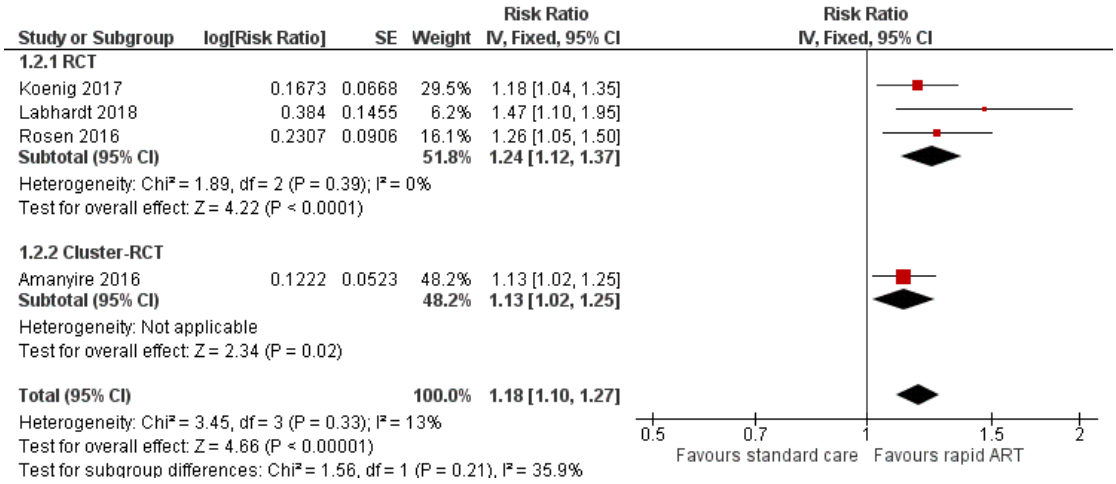


Subgroup analysis by timing of ART initiation (Analysis 2.1), showed no difference in the risk of dying if ART was initiated on the same day as diagnosis (RR 0.59, 95% CI 0.34 to 1.02, 1786 participants, 4 studies, I^2 = 0%), within seven days (RR 0.80, 95% CI 0.46 to 1.39; 2197 participants, 1 study), at the first clinic visit (RR 0.87 95% CI 0.40 to 1.89; 1031 participants, 1 study) or within 14 days after diagnosis (RR 0.65, 95% CI 0.14 to 3.02; 437 participants, 1 study).

Virological suppression

Those who initiated ART rapidly were more likely to be virally suppressed at 12 months (RR 1.18, 95% CI 1.10 to 1.27; 2719 participants, 4 studies, I^2 = 13%; moderate-certainty evidence; Analysis 1.2; Figure 6).

Figure 6. Forest plot of comparison 1. Rapid ART versus standard care, outcome 1.2, virological suppression at 12 months



There was variation in how the studies measured viral suppression. All the studies, apart from McNairy 2017 measured virological suppression in all randomized participants; McNairy 2017 assessed virological suppression only for those who had been on ART at least for six months. It was not possible to obtain the denominator of all ART-eligible participants, so we excluded this study from the analysis of this outcome. McNairy 2017 found no differences between the rapid ART group and the control group when measuring virological suppression in those on ART for at least six months (RR 0.98, 95% CI 0.93 to 1.02; Analysis 3.1).

Subgroup analysis by timing of ART initiation revealed no difference between same-day (RR 1.24, 95% CI 1.12 to 1.37; 1354 participants, 3 studies; I^2 = 0%) and 14-day ART initiation (RR 1.13, 95% CI 1.02 to 1.25; 437 participants, 1 study; Analysis 2.2).

Secondary outcomes

Retention in care

Four RCTs (Koenig 2017; Labhardt 2018; Rosen 2016; Stevens 2017), and two cluster-RCTs (Elul 2017; McNairy 2017), measured retention in care at 12 months. Those randomized to rapid ART were 22% more likely to be retained in care at 12 months (RR 1.22, 95% CI 1.11 to 1.35; 5001 participants, 6 studies; I^2 = 54%; low-certainty evidence; Analysis 1.3). There was moderate heterogeneity (I^2 = 54%), which may have been caused by the different methods used to define retention in care across studies.

The subgroup analysis by timing of ART initiation showed some difference between groups (Analysis 2.3; test for subgroup differences P = 0.05; I^2 = 66.8%). However, all subgroups showed better retention in the intervention arm.

Amanyire 2016 measured retention in care by calculating visit adherence as the mean number of visits per participant and the proportion of scheduled visits attended. They did not find any differences between the intervention and control groups (RR 1.00, 95% CI 0.99 to 1.01).

Uptake of ART at 90 days

Three RCTs (Koenig 2017; Labhardt 2018; Rosen 2016), and one cluster-RCT (Amanyire 2016), measured uptake at 90 days. Those randomized to rapid ART were more likely to start ART within 90 days of enrolment (RR 1.31, 95% CI 1.18 to 1.45; 11,404 participants, 4 studies, I^2 = 94%; low-certainty evidence; Analysis 1.4).

We investigated possible sources of clinical and methodological heterogeneity. We subgrouped by timing of ART initiation (same day versus 14 days from diagnosis), but could not explain the observed heterogeneity (Analysis 2.4).

Uptake of ART at 12 months

Those randomized to rapid ART were more likely to have started ART at 12 months compared with those who received the standard care (RR 1.09, 95% CI 1.06 to 1.12; 3713 participants, 4 studies; I^2 = 32%; moderate-certainty evidence; Analysis 1.5).

There were no differences in the subgroup analysis between those initiating ART on the same day as diagnosis, within seven days of diagnosis or at the first clinic visit (Analysis 2.5).

Treatment modification

We found that those randomized to rapid ART were more likely to experience treatment modification compared with those randomized to the standard care arm (RR 7.89, 95% CI 0.76 to 81.74; 977 participants, 2 studies; I^2 = 41%; very low-certainty evidence; Analysis 1.6).

Adverse events

One study reported adverse events (Labhardt 2018). Six participants out of 137 in the rapid ART group reported adverse events (2 experienced rash, 1 dizziness, 1 gynaecomastia, and 1 had elevated alanine aminotransferase levels). Two participants experienced adverse events (rash) in the standard care arm.

DISCUSSION

Summary of main results

See Summary of findings for the main comparison.

We included seven studies in this review: six were carried out in sub-Saharan Africa, and one study was conducted in Haiti. Four were individually RCTs with a total of 1786 participants and three were cluster-RCTs with 16,225 participants. The study population included adults aged 18 years and older from urban and rural areas. Four studies offered participants ART on the same day as diagnosis, one within seven days, another within 14 days, and another at the first clinic visit. There was substantial heterogeneity of intervention delivery methods and cointerventions. Most studies initiated ART at the health facility and one provided home-based ART initiation. Three studies distributed non-cash financial incentives, two studies used mobile phone visit reminders, one study reported opinion-leader training of health staff, several provided point-of-care CD4 testing, one provided multi-month ART prescriptions, and there were variable approaches to assessing participant 'readiness' to start ART.

Primary outcomes

Although there was some evidence of reduced mortality with rapid ART, high levels of attrition, indirectness, qualitative heterogeneity, and imprecision resulted in very low-certainty in the pooled effect estimate for this outcome. Subgrouping by study design or time to ART initiation also did not show any significant effect of rapid ART in any of these groups. Rapid ART probably improves virological suppression at 12 months. There was moderate-certainty evidence contributing to this outcome; the beneficial effect on virological suppression was seen across subgroups with variable time to ART initiation.

Secondary outcomes

Rapid ART probably improves uptake of ART at 12 months (moderate-certainty evidence), and this effect was seen across subgroups for study design and time to ART initiation. Rapid ART may also improve uptake of ART at 90 days and improve retention at 12 months, with low-certainty evidence contributing to these outcomes. Finally, we do not know if those receiving ART are more likely to experience treatment modification.

Adverse events/harms

There was insufficient evidence regarding adverse events to draw conclusions for this outcome.

Overall completeness and applicability of evidence

The included studies were conducted in adults in LMICs and therefore are only generalizable to these groups. Numerous cointerventions were also included in the delivery of rapid ART, highlighting that in order to achieve these study outcomes, several additional changes need to be made to health system structures and processes. Healthcare staff need to be trained to accelerate clinical and psychological assessments, and incentives as well as general improvements in treatment support and health worker approach may be required. Given the differences in cointerventions and how delivery modes varied across studies, the direct applicability of these results to other settings may be limited. All studies, however, demonstrated benefit, suggesting that setting-specific delivery methods, which are combined with appropriate cointerventions that enhance services and seek to reduce barriers to care are likely to result in comparable results during implementation in other settings. No studies presented long-term outcomes; we therefore cannot make inferences regarding long-term treatment outcomes based on these data. Finally, ART eligibility criteria differed across studies and only one study considered PLWH eligible for ART irrespective of CD4 count, which is the current WHO recommendation. It is possible that rapid ART's effectiveness differs in PLWH according to severity of disease, which we have not been able to analyse in this review.

Certainty of the evidence

We found methodological limitations for several outcomes that resulted in downgrading the certainty of the evidence for risk of bias. High levels of attrition across studies (ranging from 17% to 42%) could have affected mortality outcome assessments; this however was not a concern for other outcomes such as uptake, virological suppression and retention in care. All the studies were unblinded resulting in a high risk of performance bias for participants and personnel, specifically for ART uptake and retention in care at 12

months. We further downgraded the mortality, virological suppression, and retention in care outcomes for indirectness, as two studies (Elul 2017; McNairy 2017), included ART-ineligible participants in their denominators, and several cointerventions were delivered alongside rapid ART, which could impact the outcomes measured. We further downgraded for qualitative heterogeneity, as there was variation in time to ART initiation, which ranged from same-day start to initiation at 14 days after diagnosis. Marked statistical heterogeneity of the 90-day ART uptake outcome, which could not be explained by subgrouping, led to downgrading of this outcome. Finally, imprecision due to few events or wide CIs of pooled effect estimates, or both, led to downgrading of mortality, 90-day ART uptake and treatment modification outcomes.

Potential biases in the review process

We minimized bias in the review process by conducting an extensive search using a wide range of search terms and databases. Two review authors independently assessed the search results to evaluate which articles were eligible for our review. By limiting our analysis to RCTs we have minimized the risk of bias derived from non-randomized study designs. We further minimized the risk of bias in cluster-RCTs by reporting the cluster-adjusted estimates of effect when available and using appropriate methods for cluster-adjustment. Lack of data (only one study reported on adverse events) limited our ability to comment on the potential harms associated with rapid ART. We could not assess publication bias due to the limited number of studies included in the review.

Agreements and disagreements with other studies or reviews

Our synthesis supports findings from an earlier systematic review and meta-analysis conducted by Ford 2018, which similarly found that rapid ART improved uptake, virological suppression, and retention in care at 12 months. We have included an additional four studies (Elul 2017; McNairy 2017; Labhardt 2018; Stevens 2017), and have found similar or stronger associations for primary and secondary outcomes.

Findings from observational studies support results from this review and demonstrate better or similar outcomes between early and delayed ART (Table 4). Data from general adult population cohort studies have shown better uptake and time to viral suppression among those initiating ART early compared to more delayed ART initiation, and no difference in retention in care in the one cohort reporting on this outcome (Pilcher 2017). Oladele 2018 evaluated different rapid ART delivery methods and determined that community-based rapid ART was more effective than referral for facility-based rapid ART. Among pregnant women, same-day ART initiation appeared to result in similar retention or viral suppression compared to delayed treatment (median seven days; Langwenya 2018). Vogt 2017 evaluated ART initiation within seven days compared to beyond seven days in children and showed better retention and survival among early ART initiators, although numbers were small. An additional cohort study conducted in adolescents showed no significant difference on retention or mortality among those who initiated ART early compared to those with more delayed ART start (Ssebunya 2017).

AUTHORS' CONCLUSIONS

Implications for practice

Overall, interventions that include rapid initiation of antiretroviral therapy (ART) appear to improve outcomes across the HIV treatment cascade, at least in the short term. Those implementing this intervention should consider the cointerventions and health system modifications required to facilitate rapid delivery of ART and ensure effectiveness.

Implications for research

Now that rapid ART is being implemented widely, researchers need to consider what the best modes of implementation are, how to adapt health systems and what cointerventions to offer within resource constraints in order to support patients to accept ART, and link to care and remain engaged in care in the long term. Pragmatic research that helps define 'treatment readiness', explores cointerventions that are feasible, and defines treatment delivery modes within complex health system interventions will help specify how to implement rapid ART.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Amanyire 2016

Methods	Stepped-wedge, cluster-RCT in a network of 20 health facilities in Uganda
Participants	15,000 treatment-naïve participants were drawn from healthcare clinics in urban and rural areas Inclusion • All HIV-infected adults (aged ≥ 18 years). • Clinically eligible for ART (by clinical or CD4 cell count criteria) during the study period.
Interventions	Intervention group • Opinion-leader-led training and coaching of front-line health workers. • POC CD4 cell count testing platform. • A revised counselling approach without mandatory multiple pre-initiation sessions. • Feedback to the facilities on their ART initiation rates and how they compared with other facilities. Control group • Standard care.
Outcomes	ART initiation within 14, 30 and 90 days after the first date of clinical eligibility for ART, HIV RNA suppression and survival 1 year after ART eligibility; retention in care; vertical transmission; cost and cost-effectiveness
Notes	HIV RNA suppression and survival 1 year after ART eligibility were assessed in a random subsample of 437 participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was stratified by four facility levels defined by size and time offering HIV care and treatment services. Randomisation was done with a random number generator in Stata (version 13). Random allocation of clinics was done by a statistician who was not otherwise involved with the study planning or analysis"
Allocation concealment (selection bias)	Low risk	Authors mention that random allocation of clinics was carried out by a statistician who was otherwise not involved in the study planning or analysis

Amanyire 2016 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	This was a non-blinded study. The fact that participants and researchers knew the allocation group of participants could have affected the primary outcome (ART initiation) and subsequently the other secondary outcomes (virological suppression and retention in care)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	There is no information around outcome assessment. However, due to the objective nature of the outcomes (ART initiation, retention and virological suppression), it is unlikely that these would be influenced by the unblinded nature of the study
Incomplete outcome data (attrition bias)	Low risk	There were almost 3000 participants randomized who were excluded because they were not eligible for ART. The rest of the randomized participants had the primary outcome assessed. Study authors selected a subsample of 437 to follow up after a year and they were able to measure outcomes on 75% in the intervention group and 79% in the control group. It is unlikely that attrition could bias the estimate effect of the outcomes of retention in care, uptake of ART and virological suppression
Incomplete outcome data (attrition bias) Mortality	High risk	Study authors were unable to measure the outcome of mortality on 25% of the intervention group and 21% of the control group. These high rates could have biased the estimate effect of mortality
Selective reporting (reporting bias)	Low risk	The outcomes were prespecified in the protocol. They were changed to make them more specific, but they were altered before the data were collected
Other bias	Low risk	We did not identify any other risks of bias.
Recruitment bias	High risk	The fact that participants knew which clinics were allocated to the intervention alongside the prospect of receiving a higher-quality of care could have made certain groups choose an intervention clinic over a control one

Amanyire 2016 (*Continued*)

Baseline comparison concerns	High risk	There were significant imbalances between the intervention and control arms at baseline. For example, the number of participants eligible for ART was significantly higher in the control arm (61%) compared with the intervention arm (39%)
Correct statistical analysis	Low risk	Study authors took clustering into account and adjusted the results using appropriate statistical methods
Loss of clusters	Low risk	All clinics randomised were included in the final analysis
Contamination	Low risk	We considered that there is no possible herd effect that could make those PLWH who are closer to intervention clinics less likely to develop the outcomes

Elul 2017

Methods	Non-blinded, cluster-RCT. 10 clinics in Mozambique were randomized to either intervention (CIS) or control (standard care). A pre-post intervention 2-sample design was nested within the intervention arm to assess the additional effectiveness of an enhanced version of the CIS, referred to as CIS+. Consequently, the standard care arm enrolled 1 cohort of patients, while the intervention arm enrolled 2 sequential cohorts of patients (CIS and CIS+). CIS+ participants were enrolled after CIS enrolment was completed at each facility randomized to the intervention arm
Participants	5327 participants 5 clinics were selected from urban areas and 5 from rural areas Inclusion • All adults testing HIV-positive in the VCT clinics within the participating health facilities Exclusion • < 18 years of age. • Pregnant. • Planned to move from their community of residence in the next 12 months. • Had enrolled in HIV care or initiated ART in the past 6 months. • Did not understand Portuguese or Xitsua. • Were incapable of providing informed consent.
Interventions	Intervention arm: 4 evidence-based interventions that simplified the clinic flow and encouraged linkage to and retention in care: • Pima (Inverness Medical Innovations) CD4 assay machines in the VCT clinics to enable HIV testing counsellors to provide real-time, POC CD4 test results immediately following diagnosis. • Participants with Pima CD4 cell count < 350 cells/mm^3 were provided with rapid

	ART initiation. These individuals received an individual ART preparatory counselling session in the VCT clinic immediately following CD4 testing, on the day of diagnosis. Facility receptionists were instructed to expedite appointments for these participants when they presented to schedule their clinical consultations. Clinicians were encouraged to initiate ART at the first clinical visit. • Participants received health messages and appointment reminders via SMS messaging. • participants in the CIS+ cohort received the CIS interventions plus a series of non-cash FIs in the form of prepaid cellular air-time cards. Control: standard care - participants were managed as per prevailing Ministry of Health guidelines • Individuals diagnosed with HIV received post-test counselling in the VCT clinic and were referred verbally to HIV services. • Participants presenting to the facility receptionist to schedule a clinical consultation for HIV care were referred to the laboratory for CD4 cell count, chemistry, and haematology testing, and provided with an appointment 2-4 weeks later to allow sufficient time for the laboratory results to be received. • ART eligibility was determined at that first clinical consultation based on CD4 cell count < 350 cells/mm^3 and/or WHO stage 3/4. • Those found to be eligible for ART received at least 1 individual counselling session before initiating treatment. • For ART-eligible participants, the time interval between enrolment in HIV care and ART initiation was estimated at 1-2 months at the time the study started. • Participants initiating ART were requested to return every 2 weeks for the first month, at 2 months, at 6 months, and every 6 months thereafter. • ART-ineligible participants were instructed to return at 6 months for repeat clinical evaluation and laboratory testing.
Outcomes	Mortality and viral suppression at 12 months, time to ART initiation, linkage to care at 1 month, retention in care at 6 months, disease progression
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Matched pairs were randomised by one of the authors (MRL) using a computerized random number generator to either the CIS arm or the standard care arm using matched-pair randomization."
Allocation concealment (selection bias)	Low risk	Quote: "Sequences were concealed until interventions were assigned."
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was non-blinded. The fact that participants knew that they were taking part in an experimental study could affect

		their performance in relation to primary outcomes (linkage and retention in care) as well as some of the secondary outcomes (for example, ART initiation)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes assessed through the electronic medical records of participants are at low risk of detection bias
Incomplete outcome data (attrition bias)	Low risk	Although LTFU rates were high (42% and 56% in the intervention and control group) , attrition is unlikely to affect the outcomes of retention in care, uptake of ART and virological suppression
Incomplete outcome data (attrition bias) Mortality	High risk	The high LTFU rates and the significant differences between the intervention and control group means that attrition could bias the estimate of effect of mortality
Selective reporting (reporting bias)	Low risk	Study outcomes have been described in the published protocol
Other bias	Low risk	We did not identify any other risks of bias.
Recruitment bias	High risk	Clinics were matched by various characteristics, including setting (urban and rural) . There isn't enough information to know where exactly the clinics were situated. But there is a possibility that PLWH decided to attend a clinic with the intervention because they knew of the package of care that was offered Recruitment continued after randomization, potentially affecting the recruitment. However baseline characteristics between intervention and comparator arm are similar
Baseline comparison concerns	Low risk	There were no significant imbalances between groups at baseline assessment
Correct statistical analysis	Low risk	The study authors took clustering into account and adjusted the results using appropriate statistical methods
Loss of clusters	Low risk	All clinics randomised were included in the final analysis

Elul 2017 (*Continued*)

Contamination	Low risk	There is no possible herd effect that could make those PLWH who are closer to intervention clinics less likely to develop the outcomes

Koenig 2017

Methods	Open-label RCT in Haiti
Participants	762 participants Inclusion • Age ≥18 years. • Ability and willingness of participant to give written informed consent. • CD4 cell count ≤ 500 cells/mm^3. • WHO stage 1 or 2 disease. Exclusion • Any use of ART in the past. • Pregnancy or breastfeeding at the screening visit. • Psychologically unprepared to start ART, based on ART readiness survey. • Plans to transfer care to another clinic during the study period. • WHO stage 3 or 4 disease.
Interventions	Intervention • Day of presentation: HIV testing, CD4 count, physician evaluation, first adherence counselling visit with social worker; physician visit for ART initiation and ART initiation. • Days 3, 10 and 17: first, second and third adherence counselling visits with social worker; physician visit to assess for opportunistic infections and provide adherence counselling. • Day 24 and Week 7: physician visits for medical assessment and adherence counselling. • Participants also had prophylactic treatment with trimethoprim-sulphamethoxazole and isoniazid. Field workers phoned participants who missed a visit and attempted a home visit for those not reachable by phone. Control • Days 7, 14: first and second adherence counselling visits with social worker; physician visit to assess for opportunistic infections and provide adherence counselling. • Day 21: third adherence counselling visit with social worker; physician visit for ART initiation. • Week 5: fourth adherence counselling visit with social worker; physician visit to assess for opportunistic infections and provide adherence counselling. • Week 7: physician visit for medical assessment and adherence counselling.
Outcomes	Retention in care at 12 months, viral suppression at 12 months, adherence to ART, uptake of ART, cost-effectiveness of standard and same-day ART initiation
Notes	

Koenig 2017 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomly assigned with the use of a computer-generated random-number list to either standard ART or same-day ART initiation in a 1:1 ratio, with allocation concealment. The randomization sequence was generated by a computer in the GHESKIO data management unit by a data manager who had no other involvement in study procedures"
Allocation concealment (selection bias)	Low risk	Authors mention that "Participants were randomly assigned with the use of a computer-generated random-number list to either standard ART or same-day ART initiation in a 1:1 ratio, with **allocation concealment**". However, there is not description of the method used for allocation concealment, and therefore it is not possible to assess in detail how valid it was
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was an open-label study. Quote: "Participants, site personnel, and study statisticians were not masked to group assignment." The main outcome was retention in care with viral suppression. LTFU was defined as "failure to attend the 12-month visit." If participants knew that they were allocated to the experimental arm of a new trial, they may have been more likely to attend the follow-up visit The same argument is valid for the secondary outcomes of uptake and adherence
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were defined objectively and did not rely on subjective reports. So, the fact that assessors knew the allocation group of participants is unlikely to have affected the assessment
Incomplete outcome data (attrition bias)	Low risk	Study authors used a "modified intention-to-treat approach. .., in which all patients were analysed according to their assignment group, excluding patients who transferred to another facility during the follow-up period, according to protocol." The number of participants excluded due to transfer to another facility was 28/384 in the control group and 31/378 in the intervention group The number of participants LTFU in the intervention group was 17% and in the control group 23% Given that a similar number of participants across groups were excluded for the same reason and that "Plans to transfer

Koenig 2017 (*Continued*)

		to another clinic" was an exclusion criteria pre-defined in the protocol, the risk of attrition bias is low
Incomplete outcome data (attrition bias) Mortality	Low risk	Quote: "Vital status at the end of the study was known for 328 (92%) participants in the standard ART group and 329 (95%) in the same-day ART group." Therefore, the risk of attrition bias is low.
Selective reporting (reporting bias)	Low risk	The primary outcomes pre-specified in the protocol were reported Study authors added a number of outcomes that were not in the original protocol • retention with undetectable viral load at < 200 copies/mL and < 1000 copies/mL cut-off points. Only reported at < 1000 copies/mL and not at < 200 copies/mL • proportion of participants who initiate ART during the study period. However, it is highly unlikely that the outcome < 200 copies/mL would give any additional or relevant information not captured by the other thresholds reported
Other bias	High risk	Selection bias: quote, "Patients were excluded if failed to demonstrate preparedness on an ART readiness survey, which was administered by a social worker prior to study enrolment. The survey includes a 5-point scale, with respondents ranking their preparedness from "not at all ready" to "completely ready" in response to 7 questions. Study inclusion required a response of "somewhat ready" or "completely ready" for all 7 questions"

Labhardt 2018

Methods	Multicenter, 2-group, open-label RCT in Lesotho
Participants	278 participants randomized from 268 households Inclusion • HIV infection newly diagnosed during community-based HIV testing and counselling (HTC)-campaign. • Never been on triple-ART. • Lived and/or worked in the district of Butha-Buthe and declared to seek follow-up at one of the 6 health facilities involved in the study. • Signed written informed consent. Exclusion • Pregnant or breast-feeding. • Already enrolled in chronic care for another disease, such as TB or diabetes. • Clinical WHO-stage 4 or active tuberculosis. • Positive cryptococcal antigen test.

Interventions	Intervention arm: In the same-day group • Participants were offered same day ART initiation. • Participants received pre-ART counselling directly after testing, accompanied by a leaflet that summarized the key points of ART adherence. • If they agreed to start therapy within the upcoming days, the study nurse left a 30-day supply of ART. • Once participants linked to care at the health facility and had their first health facility visit (including ART dispensing), they followed the usual care for ART patients with the exception of longer intervals between follow-up visits (1.5, 3, 6, 9, and 12 months after ART start). Control arm: participants randomized to the usual care group followed the usual care provided in Lesotho, which is similar to most settings in southern Africa • They received post-test counselling in the home and an appointment at their nearest health facility within the next 28 days. • Once linked to care, they had to undergo at least 2 pre-ART health facility visits. • During the first health facility visit, blood was drawn for baseline laboratory work and a first pre-ART counselling session was conducted. • At the second health facility visit, laboratory results were communicated and the participant's readiness to start ART was assessed. • Depending on the judgment of the health facility staff, the participant was offered to start ART. • Once ART was started, the participants were given monthly follow-up and drug refill dates.
Outcomes	Mortality, virological suppression and retention in care at 12 months, uptake of ART and number of visits attended
Notes	Study authors effectively randomized households, as they mention that households with > 1 eligible individual were automatically allocated to the same group to reduce contamination between the groups. However, we treated it as an individual RCT as only 10 households (5 in each arm) had 2 participants)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "A computer-generated randomization list was generated in block sizes of 4."
Allocation concealment (selection bias)	Low risk	Quote: "A separate person, not involved in the trial, prepared the sealed, sequentially numbered, opaque envelopes. The study nurse allocated participants to a group by opening the next sealed envelope in the sequence"
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was an open-label trial. Participants' performance, including attending health facilities and adherence to

		treatment, could be influenced by knowing that they were being part of the experimental arm of a research study. This could have an effect on all the primary and secondary outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary and secondary outcomes were objectively assessed and did not rely on self-reports. Therefore, the risk of detection bias is low
Incomplete outcome data (attrition bias)	Low risk	Outcome group: all/quote: "Patients were analysed according to their randomization group following an intention-to-treat protocol" LTFU were 8.8% in the intervention group and 7.3% in the control group. As rates were low and similar in both groups, the risk of attrition bias is low
Incomplete outcome data (attrition bias) Mortality	Low risk	LTFU were low and there were not significant different across groups. Therefore, it is unlikely that attrition could bias the estimate effect of mortality
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were prespecified in the protocol. Therefore the risk of reporting bias is low
Other bias	Low risk	No other sources of bias were identified.

McNairy 2017

Methods	Open-label cluster-RCT. 10 units were selected from a total of 11 existing secondary-level HIV clinics in Swaziland (today known as eSwatini). These units were pair-matched by implementing partner, location and clinic size
Participants	2550 individuals from 10 clinics Inclusion criteria • Age ≥ 18 years. • Testing HIV-positive at an HTC site within a SU. • Willing to be referred to an HIV care clinic associated with the SU. • Willing to provide locator information. • Willing to adhere to study procedures, including a baseline interview, home-based interviews at 1 and 12 months after study enrolment; home-based CD4+ count assessment 12 months after enrolment, and abstraction of data from their medical records. • Able to provide informed consent. Exclusion criteria

	• Planning on leaving the community where they currently reside in the next 12 months for a period > 6 months. • Enrolled in HIV care in the past 6 months at any HIV care clinic. • Currently on ART. • Initiated ART (for any duration) in the past 6 months at any HIV care clinic. • Does not speak or understand English or si-Swati. • Reports being currently pregnant at time of study enrolment.
Interventions	Intervention arm - CIS: participants received a multi component strategy of 5 evidence-based interventions • POC CD4+ count. • Accelerated ART initiation. • Cellular phone visit reminders. • Health education packages. • Non-cash FIs. Control arm: managed according to country guidelines. • Received post-test counselling. • Referred to an HIV clinic using a national referral form. • At first HIV clinic visit participants have: ○ clinical assessment ○ blood drawn for a CD4+ count test ○ hematology tests ○ chemistry tests ○ instructions to return 1-2 weeks later for test results. • At return visit, participants eligible for ART according to then prevailing national guidelines (i.e. with a CD4+ count ≤ 350 cells/mm^3) ○ have first of 3 counselling sessions ○ are instructed to return to the clinic every month for 6 months and then every 3 months, if they are stable on treatment. • Participants ineligible for ART ○ instructed to return to clinic every 3 months for follow-up. • Peer counsellors are encouraged to call participants within 7 days of a missed clinic appointment. All participants prescribed cotrimoxazole prophylaxis, and condoms, and health informational materials made available in the clinics
Outcomes	Primary outcome • Linkage to HIV care within 1 month of HIV testing. • Retention in care at 12 months from HIV testing. Secondary outcomes • Time to linkage of care. • ART eligibility. • ART initiation. • Time to ART initiation. • Viral suppression among participants on ART for at least 6 months. • Death at 12 months. • LTFU at 12 months.
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Matched study units were randomised by a computerized random number generator to the CIS or standard care (SC) study arm"
Allocation concealment (selection bias)	Low risk	This is a cluster-RCT. Clusters were randomized before participants were recruited and therefore allocation concealment was not possible. Possible bias due to baseline imbalances are described below
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was an open-label trial. The fact that the personnel in the clinics and the participants knew that they were taking part in an experimental trial could have had an impact on the primary outcomes (linkage of care and retention in care) as well as on the secondary outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcomes were objective and not susceptible to interpretation of assessors. Therefore, the risk of detection bias is low
Incomplete outcome data (attrition bias)	Low risk	There were high rates of LTFU (29% in intervention group and 49% in control). However it is unlikely that attrition could bias the estimate of effect of the outcomes of retention in care, uptake of ART and virological suppression
Incomplete outcome data (attrition bias) Mortality	High risk	LTFU rates were > 25% in both groups and significantly higher in the control arm. This could have had an impact on the estimate of effect of the primary outcome of mortality
Selective reporting (reporting bias)	Low risk	Outcomes were pre-specified in the protocol and reported in the study. There were some outcomes not reported, but this is likely due incomplete data rather than selective reporting
Other bias	Low risk	We did not identify any other risks of bias.

McNairy 2017 (*Continued*)

Recruitment bias	High risk	Clinics were matched by various characteristics, including setting (urban and rural). There is not enough information to know where exactly the clinics were situated. But there is a possibility that PLWH decided to attend a clinic with the intervention because they knew of the package of care that was offered
Baseline comparison concerns	Low risk	Overall, there were no big baseline imbalances. Lower weekly income in the intervention group and higher rate of unemployment, but significantly closer to the clinics than those in the control group
Correct statistical analysis	Low risk	Study authors took clustering into account and adjusted the results using appropriate statistical methods
Loss of clusters	Low risk	All clinics randomised were included in the final analysis
Contamination	Low risk	There is no possible herd effect that could make those PLWH who are closer to intervention clinics less likely to develop the outcomes

Rosen 2016

Methods	Open-label RCT in South Africa
Participants	463 participants were recruited from 2 sector outpatient clinics. 1 site was a primary health clinic serving an urban informal settlement population on the edge of Johannesburg. The second was a large hospital-based HIV clinic serving an urban formal and informal population within Johannesburg Inclusion criteria • Adult patients (> 18 years). • Tested HIV-positive at study site's outpatient testing service or antenatal clinic on day of study enrolment or previously tested HIV-positive but making first visit to study site for HIV-related care or antenatal care for the current pregnancy. • Eligible for ART under prevailing South African guidelines. Exclusion criteria • Currently or previously on ART (3-drug combination; previous prevention of mother-to-child transmission (PMTCT) regimen exposure for an earlier pregnancy is not an exclusion criterion). • Stated intention to seek further HIV or antenatal care at another site, not at the study site. • Not physically or emotionally able to participate in the study, in the opinion of

	the investigators. • Not willing or able to provide written informed consent to participate in the study. • Previously screened for the same study.
Interventions	Intervention • All the normal procedures (for example, CD4+ count, TB symptom screen and test...), including ART initiation, were carried out during the first clinic visit. Control arm • Standard care according to South African guidelines. • 6 clinic visits before ARTs are dispensed.
Outcomes	Primary outcome • Viral suppression at 10 months. Secondary outcomes • Retention in care at 10 months. • Initiation of treatment within 90 days of study enrolment. • Uptake of treatment within 180 days. • Time to treatment initiation.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Participants were individually randomised 1:1 to either rapid treatment initiation or standard-of-care treatment initiation, using block randomization in blocks of 6" Although they mention block randomization, they do not describe the methods used to generate sequence generation. Therefore, it is unclear if the sequence generation method was truly random
Allocation concealment (selection bias)	Low risk	Quote: "Sealed, opaque envelopes containing the allocations were prepared by the local principal investigator and numbered sequentially. The envelopes were kept in sequential, numbered order at the study sites. After obtaining written informed consent, the study assistant opened the next sequentially numbered envelope to reveal the allocation."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote from text: "RapIT (Rapid Initiation of Treatment) was an unblinded, individually randomised, controlled trial of a service delivery intervention." This trial was unblinded and it could cause an improvement of uptake and adherence to ART in those participants allocated to the experimental arm because they were aware that they were part of the ex-

		perimental group. A hugely improved standard care was achieved in the intervention arm. The increase in uptake and adherence could affect all the outcomes measured, including virological suppression, causing performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcomes were assessed through retrospective electronic medical records. Furthermore, the outcomes were objective and not self-reported. For this reason, it is unlikely that they were subject to detection bias
Incomplete outcome data (attrition bias)	Low risk	LTFU was 19% in the rapid arm and 36% in the control arm. Although LTFU rates were high and not balanced across groups, authors assumed that those LTFU had a negative outcome: "Finally, to confirm that no imbalance was created by excluding patients after randomization for reasons other than ineligibility for ART or evidence of a previous eligible CD4 count, we conducted sensitivity analysis incorporating the excluded patients and assigning each a negative outcome" It is reasonable to assume that PLWH who were LTFU were not retained in care, did not start ART and were not virally suppressed
Incomplete outcome data (attrition bias) Mortality	High risk	LTFU was 19% in the rapid arm and 36% in the control arm. LTFU was significantly higher in the control arm. This could have had an impact on the estimate of effect of the primary outcome of mortality
Selective reporting (reporting bias)	Low risk	The outcomes reported were pre-specified in the protocol. Not all the outcomes in the protocol were reported in this paper. This is likely due to the trial still being ongoing
Other bias	High risk	The study included participants who accessed the clinic for a CD4 count. This means that they knew their diagnosis in advance before being enrolled in the study. This is a significantly different population compared with the ones that the review is interested (people who have been just diagnosed with HIV)

Stevens 2017

Methods	Individual RT in South Africa
Participants	717 participants were recruited from 3 primary health clinics operating under control of the North West Provincial Department of Health, from 3 separate provinces (Gauteng Province, Free State Province and North West Province) Inclusion criteria • Adults aged ≥ 18 years. • Positive HIV test. Exclusion criteria • Not being able to be followed up at the clinics for at least 12 months after treatment initiation. • CD4 count > 350 cells/mL.
Interventions	Intervention arm • POC testing for HIV. • CD4 count. • Liver and kidney function. • Expedited TB testing. • Participants eligible for ART were offered ART initiation on the same day of presentation. Control arm • Standard care as per South African national guidelines. • ART initiation between 14-21 days after presentation.
Outcomes	Primary outcomes • Proportion of PLWH initiating ART. • Median time to ART initiation. • Retention in ART care at 6 and 12 months.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A pooled-box randomization was performed using an automated web-based algorithm that generated unique numbers with allocation for an anticipated 1000 participants to either the SC or POC arm (500 to SC and 500 to POC)."
Allocation concealment (selection bias)	Unclear risk	Study authors do not mention methods of allocation concealment (for example, use of opaque, sealed envelopes)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were aware of the allocation arm of participants. If participants knew their allocation arm, they may have been more likely to uptake ART or to attend follow-up visits, compared with those in the control arm, affecting the outcomes of "Reten-

Stevens 2017 (*Continued*)

		tion in care" and "ART initiation"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study authors do not mention if outcome assessment was blinded. However, the nature of the outcomes and the fact that they were assessed objectively means that the risk of detection bias is low
Incomplete outcome data (attrition bias)	Low risk	LTFU rates were similar in both arms (68% in both arms at the end of the study). Although these rates are high, they are unlikely to have caused attrition bias for the two primary outcomes: ART initiation and retention in care
Incomplete outcome data (attrition bias) Mortality	Low risk	Many of the LTFU participants might have died and there might have been under-ascertainment of the mortality outcome: the study did however make additional efforts to determine mortality: "Records of participants not attending scheduled patient visits were logged and study staff made attempts to contact participants telephonically to ascertain location. Further follow-up was obtained, where possible, from the National Population Register (vital register) and the Central Data Warehouse of the NHLS". Given these efforts and the fact that overall mortality was about 3%-5%, which approximates mortality in cohorts where there is complete vital status ascertainment through tracing - we judged this outcome low risk of bias
Selective reporting (reporting bias)	Low risk	There was no information about pre-specified outcomes, as no reference to the protocol is found in the study. However all relevant and non-significant outcomes were reported
Other bias	Low risk	We did not identify any other risks of bias.

Abbreviations: ART: antiretroviral therapy; CIS: combination intervention strategy; FI: financial incentive; HTC: HIV testing and counselling; LTFU: loss/lost to follow-up; PLWH: people living with HIV; POC: point-of-care; RCT: randomized controlled trial; RNA: ribonucleic acid; SMS: short message service; SC: standard care; SU: study unit; TB: tuberculosis; VCT: voluntary counselling and testing.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Achhra 2017	Wrong intervention. ART initiation is not based on time since diagnosis, but on CD4 count
Bisson 2013	Wrong patient population. They only included PLWH with cryptococcal meningitis
Blanc 2011	Wrong patient population. They only included PLWH with TB.
Boulware 2014	Wrong patient population. They only included PLWH with TB.
Danel 2015	Wrong intervention. ART initiation was not based on time since diagnosis, but on CD4 count
Degu 2012	Wrong patient population. They only included PLWH with TB.
Ford 2016	Wrong study design. Not a RCT
Grant 2010	Wrong study design. Not a RCT
Havlir 2011	Wrong patient population. They only included PLWH with cryptococcal meningitis
Iwuji 2017	Wrong intervention. ART initiation was not based on time since diagnosis, but on CD4 count
Koenig 2011	Wrong design. Cost-effectiveness analysis
Larmarange 2016	Wrong intervention. ART initiation was not based on time since diagnosis, but on CD4 count
Laurelliard 2013	Wrong patient population. They only included PLWH with TB.
Long 2017	Wrong study design. Cost-defectiveness analysis
Makadzange 2010	Wrong patient population. They only included PLWH with cryptococcal meningitis
Plazy 2016	Wrong intervention. ART initiation was not based on time since diagnosis, but on CD4 count
Sabapathy 2017	Wrong intervention. ART initiation was not based on time since diagnosis, but on CD4 count
Temprano 2015	Wrong intervention. ART initiation was not based on time since diagnosis, but on CD4 count
Wu 2017	Wrong intervention. Rapid ART not part of the intervention

Abbreviations: ART: antiretroviral therapy; PLWH: people living with HIV; RCT: randomized controlled trial; TB: tuberculosis.

Characteristics of ongoing studies *[ordered by study ID]*

Maskew 2018

Trial name or title	Same-day ART initiation in the slate trial in South Africa: preliminary results
Methods	Individual RCT
Participants	PLWH attending 3 public outpatient clinics
Interventions	Intervention • A clinical algorithm (SLATE) that allows nurses to determine eligibility for immediate ART dispensing. Control • Standard care.
Outcomes	ART initiation ≤ 28 days of study
Starting date	6 March 2017
Contact information	sbrosen@bu.edu
Notes	

NCT02776254

Trial name or title	Differentiated care for improved health systems efficiency and health outcomes in Zambia (CommART)
Methods	Parallel-RCT
Participants	Inclusion criteria • HIV-positive adolescents and adults (> 14 years of age). • Last CD4 count (obtained within the last six months) > 200 cells/μL. • Not acutely ill. • For CAGs, UAGs, and fast-track models: on ART for at least 6 months. • For the START model: ART naïve and meet the Zambian HIV guidelines for treatment initiation. Exclusion criteria • For CAGs, UAGs: inability to participate in the group activities due to cognition deficits or mental illness. • Unable to provide consent or unwilling to participate in study. • Pregnancy.
Interventions	The START model aims to deliver a higher intensity of treatment services by offering same-day CD4 testing and results, streamlined adherence counselling, and quicker initiation of life-long ART to patients enrolling in HIV care and treatment services
Outcomes	Primary outcome: Retention in care at 12 months
Starting date	March 2016
Contact information	Izukanji.Sikazwe@cidrz.org

NCT02776254 (*Continued*)

Notes	

PACTR201706002322546a

Trial name or title	Early initiation ART adherence clubs versus standard care to enhance patient retention in care: a pilot study
Methods	Parallel-RCT
Participants	PLWH Inclusion criteria • Age > 18 years. • ART-naïve. • Started on ART on day of HIV diagnosis. • CD4 > 200 cells/μL. • Normal baseline blood tests (creatinine, haemoglobin, liver function tests, hepatitis B surface antigen). Exclusion criteria • Age < 18 years. • Previously on ART. • Presumed TB or receiving TB treatment. • Pregnant women. • Current comorbidity or chronic illness that is unstable (hypertension, diabetes, epilepsy, cancer, mental illness) or other disease that required routine and frequent clinical management. • Contraindicatd for fixed-dose combination ART. • Refused same-day ART initiation. • CD4 count < 200 cells/μL. • Anaemia. • Abnormal kidney or liver function tests. • Severe side effects to ART.
Interventions	Intervention • Early ART initiation clubs (early initiation clubs consist of 20-30 people with HIV who have just been diagnosed and are starting ART). Control • Standard care.
Outcomes	Proportion of participants retained in care after 6 months following ART initiation
Starting date	1 April 2017
Contact information	joels@witkoppen.co.za
Notes	

PACTR201706002322546b

Trial name or title	Early initiation ART adherence clubs versus standard care to enhance patient retention in care: a pilot study
Methods	Parallel-RCT
Participants	PLWH Inclusion criteria • Age > 18 years. • ART-naïve. • Started on ART on day of HIV diagnosis. • CD4 > 200 cells/µL. • Normal baseline blood tests (creatinine, haemoglobin, liver function tests, hepatitis B surface antigen). Exclusion criteria • Age < 18 years. • Previously on ART. • Presumed TB or receiving TB treatment. • Pregnant women. • Current comorbidity or chronic illness that is unstable (hypertension, diabetes, epilepsy, cancer, mental illness) or other disease that required routine and frequent clinical management. • Contraindicatd for fixed-dose combination ART. • Refused same-day ART initiation. • CD4 count < 200 cells/µL. • Anaemia. • Abnormal kidney or liver function tests. • Severe side effects to ART.
Interventions	Intervention • Early ART initiation clubs (early initiation clubs consist of 20-30 people with HIV who have just been diagnosed and are starting ART). Control • Standard care.
Outcomes	Proportion of participants retained in care after 6 months following ART initiation
Starting date	1 April 2017
Contact information	joels@witkoppen.co.za
Notes	

Rosen 2017

Trial name or title	Simplified algorithm for treatment eligibility (SLATE)
Methods	Open-label RCT
Participants	Inclusion • Adult patients (> 18 years) (initiating children on ART is likely to require additional information, making the SLATE algorithm less applicable to paediatric populations) • Confirmed HIV-positive test result at any time (may have been diagnosed previously)

Rosen 2017 (*Continued*)

	• Not currently on ART (3-drug combination) • Presented at the study clinic for any HIV-related reason, including an HIV test, pre-ART monitoring, or ART initiation
Interventions	Intervention • Immediate treatment initiation under the intervention algorithm (SLATE). Control • Standard procedures for initiating ART for HIV.
Outcomes	Primary outcomes • Proportion of participants initiated on ART within 28 days of study enrolment. • Proportion of participants who initiate ART within 28 days of study enrolment and are alive, in care, and retained on ART 8 months after study enrolment. Secondary outcomes • Proportion of participants who initiate ART within 14 days of study enrolment. • Proportion of participants who are virally suppressed according to local guidelines within 8 months of study enrolment. • Retention defined as > 1 month late for last scheduled visit. • Retention defined as > 3 months late for last scheduled visit. • Proportions of HIV-positive people presenting at study clinics and not yet on ART who are eligible and ineligible for immediate initiation using SLATE algorithm criteria. • Reasons for ineligibility for immediate initiation, among those found ineligible in the intervention arm. • Average time to ART initiation (days) for each arm.
Starting date	6 March 2017
Contact information	sbrosen@bu.edu
Notes	

Sikazwe 2018

Trial name or title	A streamlined ART initiation algorithm of care reduces time to ART
Methods	Unknown
Participants	Participants were from 2 urban public health facilities
Interventions	Intervention • Revised ART initiation approach with same-day readiness assessment. • POC CD4 assessment and ART initiation. Control • Standard care.
Outcomes	• Mortality. • Time to ART initiation.
Starting date	Unknown

Sikazwe 2018 (*Continued*)

Contact information	Izukanji.Sikazwe@cidrz.org
Notes	

Abbreviations: ART: antiretroviral therapy; CAG: community adherence group; PLWH: people living with HIV; POC: point-of-care; RCT: randomized controlled trial; TB: tuberculosis; UAG: urban adherence group.

DATA AND ANALYSES

Comparison 1. Rapid ART versus standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	7		Risk Ratio (Fixed, 95% CI)	0.72 [0.51, 1.01]
1.1 RCT	4		Risk Ratio (Fixed, 95% CI)	0.59 [0.34, 1.02]
1.2 Cluster-RCT	3		Risk Ratio (Fixed, 95% CI)	0.81 [0.52, 1.24]
2 Virological suppression at 12 months	4		Risk Ratio (Fixed, 95% CI)	1.18 [1.10, 1.27]
2.1 RCT	3		Risk Ratio (Fixed, 95% CI)	1.24 [1.12, 1.37]
2.2 Cluster-RCT	1		Risk Ratio (Fixed, 95% CI)	1.13 [1.02, 1.25]
3 Retention in care	6		Risk Ratio (Random, 95% CI)	1.22 [1.11, 1.35]
3.1 RCT	4		Risk Ratio (Random, 95% CI)	1.16 [1.06, 1.28]
3.2 Cluster-RCT	2		Risk Ratio (Random, 95% CI)	1.37 [1.20, 1.57]
4 Uptake of ART at 90 days	4		Risk Ratio (Random, 95% CI)	1.31 [1.18, 1.45]
4.1 RCT	3		Risk Ratio (Random, 95% CI)	1.41 [1.12, 1.76]
4.2 Cluster-RCT	1		Risk Ratio (Random, 95% CI)	1.27 [1.25, 1.29]
5 Uptake of ART at 12 months	4		Risk Ratio (Fixed, 95% CI)	1.09 [1.06, 1.12]
5.1 RCT	2		Risk Ratio (Fixed, 95% CI)	1.09 [1.06, 1.12]
5.2 Cluster-RCT	2		Risk Ratio (Fixed, 95% CI)	1.18 [1.04, 1.35]
6 Treatment modification	2	977	Risk Ratio (M-H, Random, 95% CI)	7.89 [0.76, 81.74]

Comparison 2. Rapid ART versus standard care: subgroup analysis by time of ART initiation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	7		Risk Ratio (Fixed, 95% CI)	Subtotals only
1.1 Same-day ART	4		Risk Ratio (Fixed, 95% CI)	0.59 [0.34, 1.02]
1.2 ART offered within 7 days	1		Risk Ratio (Fixed, 95% CI)	0.80 [0.46, 1.39]
1.3 ART offered at first clinic visit	1		Risk Ratio (Fixed, 95% CI)	0.87 [0.40, 1.89]
1.4 ART offered within 14 days	1		Risk Ratio (Fixed, 95% CI)	0.65 [0.14, 3.02]
2 Virological suppression at 12 months	4		Risk Ratio (Fixed, 95% CI)	Subtotals only
2.1 Same-day ART	3		Risk Ratio (Fixed, 95% CI)	1.24 [1.12, 1.37]
2.2 ART offered within 14 days	1		Risk Ratio (Fixed, 95% CI)	1.13 [1.02, 1.25]
3 Retention in care	6		Risk Ratio (Fixed, 95% CI)	Subtotals only
3.1 Same-day ART	4		Risk Ratio (Fixed, 95% CI)	1.15 [1.08, 1.23]
3.2 ART offered within 7 days	1		Risk Ratio (Fixed, 95% CI)	1.48 [1.18, 1.86]
3.3 ART offered at first clinic visit	1		Risk Ratio (Fixed, 95% CI)	1.32 [1.12, 1.56]

4 Uptake of ART at 90 days	4	Risk Ratio (Random, 95% CI)	Subtotals only
4.1 Same-day ART	3	Risk Ratio (Random, 95% CI)	1.41 [1.12, 1.76]
4.2 ART offered within 14 days	1	Risk Ratio (Random, 95% CI)	1.27 [1.25, 1.29]
5 Uptake of ART at 12 months	4	Risk Ratio (Random, 95% CI)	Subtotals only
5.1 Same-day ART	2	Risk Ratio (Random, 95% CI)	1.12 [1.02, 1.24]
5.2 ART offered within 7 days	1	Risk Ratio (Random, 95% CI)	1.16 [0.96, 1.40]
5.3 ART offered at first clinic visit	1	Risk Ratio (Random, 95% CI)	1.20 [1.00, 1.44]

Comparison 3. Rapid ART versus standard care, virological suppression: analysis by method of measurement

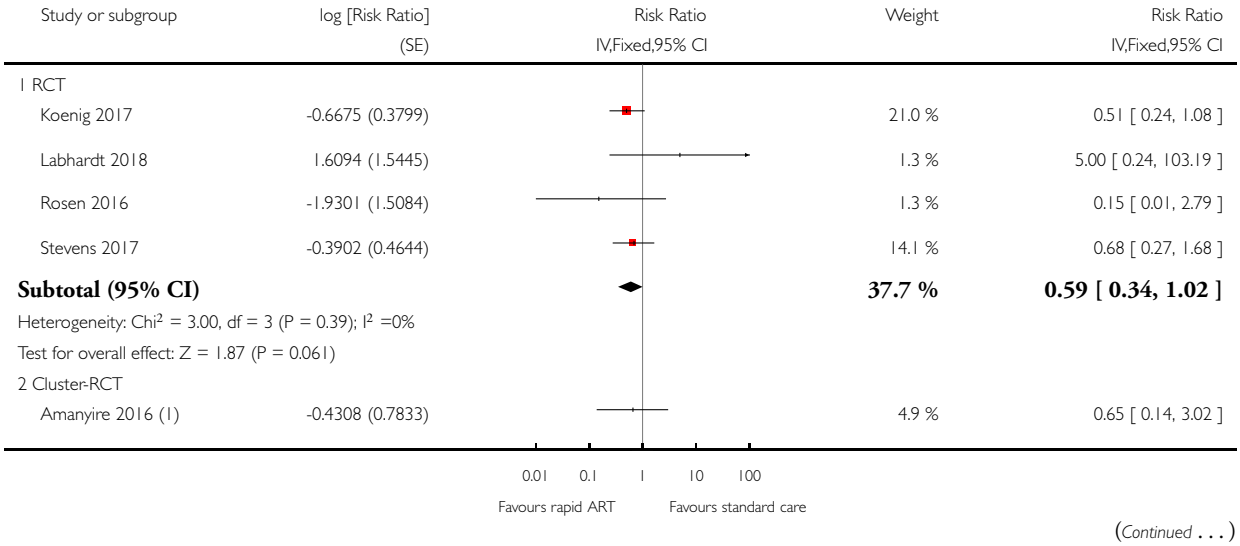
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Virological suppression at 12 months in participants on ART for at least 6 months	1		Risk Ratio (Fixed, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 Rapid ART versus standard care, Outcome 1 Mortality.

Review: Rapid initiation of antiretroviral therapy for people living with HIV

Comparison: 1 Rapid ART versus standard care

Outcome: 1 Mortality



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Elul 2017 (2)	-0.1393 (0.3965)		19.3 %	0.87 [0.40, 1.89]
McNairy 2017	-0.2231 (0.2823)		38.1 %	0.80 [0.46, 1.39]
Subtotal (95% CI)			**62.3 %**	**0.81 [0.52, 1.24]**
Heterogeneity: Chi^2 = 0.11, df = 2 (P = 0.95); I^2 =0.0%				
Test for overall effect: Z = 0.97 (P = 0.33)				
Total (95% CI)			**100.0 %**	**0.72 [0.51, 1.01]**
Heterogeneity: Chi^2 = 3.90, df = 6 (P = 0.69); I^2 =0.0%				
Test for overall effect: Z = 1.92 (P = 0.055)				
Test for subgroup differences: Chi^2 = 0.78, df = 1 (P = 0.38), I^2 =0.0%				

(1) Based on a random sample of participants which was inverse probability weighted

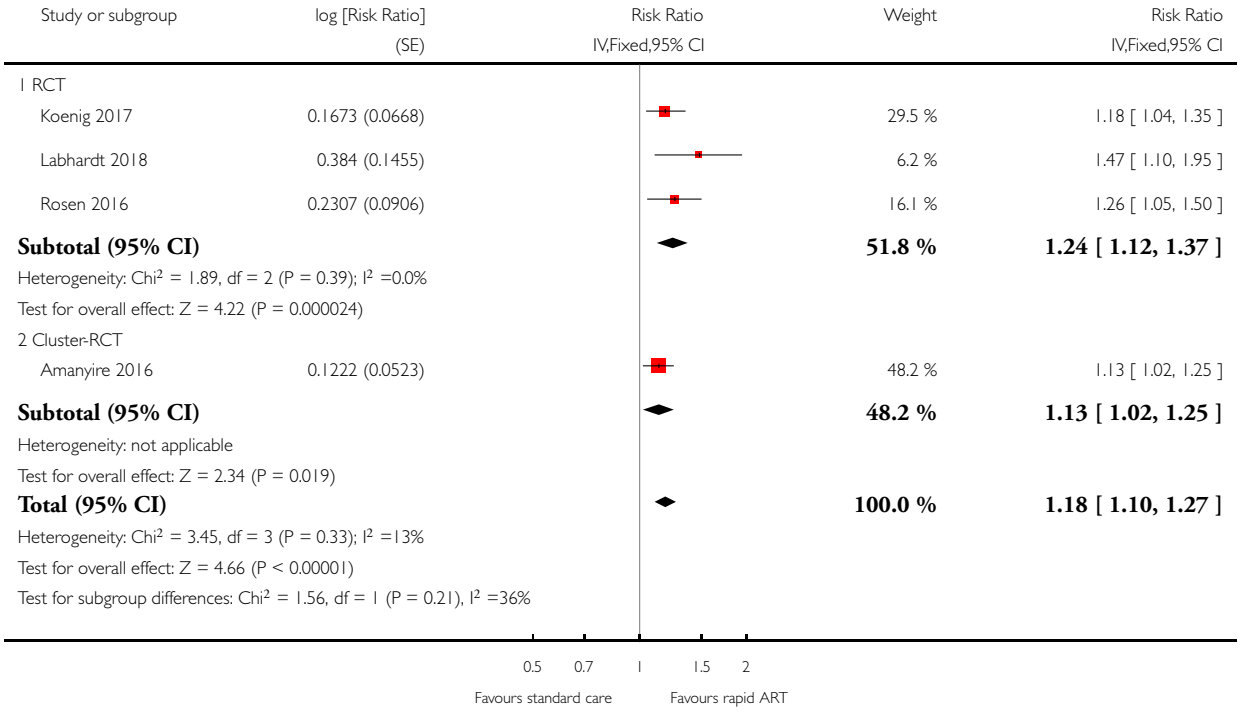
(2) CIS

Analysis 1.2. Comparison 1 Rapid ART versus standard care, Outcome 2 Virological suppression at 12 months.

Review: Rapid initiation of antiretroviral therapy for people living with HIV

Comparison: 1 Rapid ART versus standard care

Outcome: 2 Virological suppression at 12 months

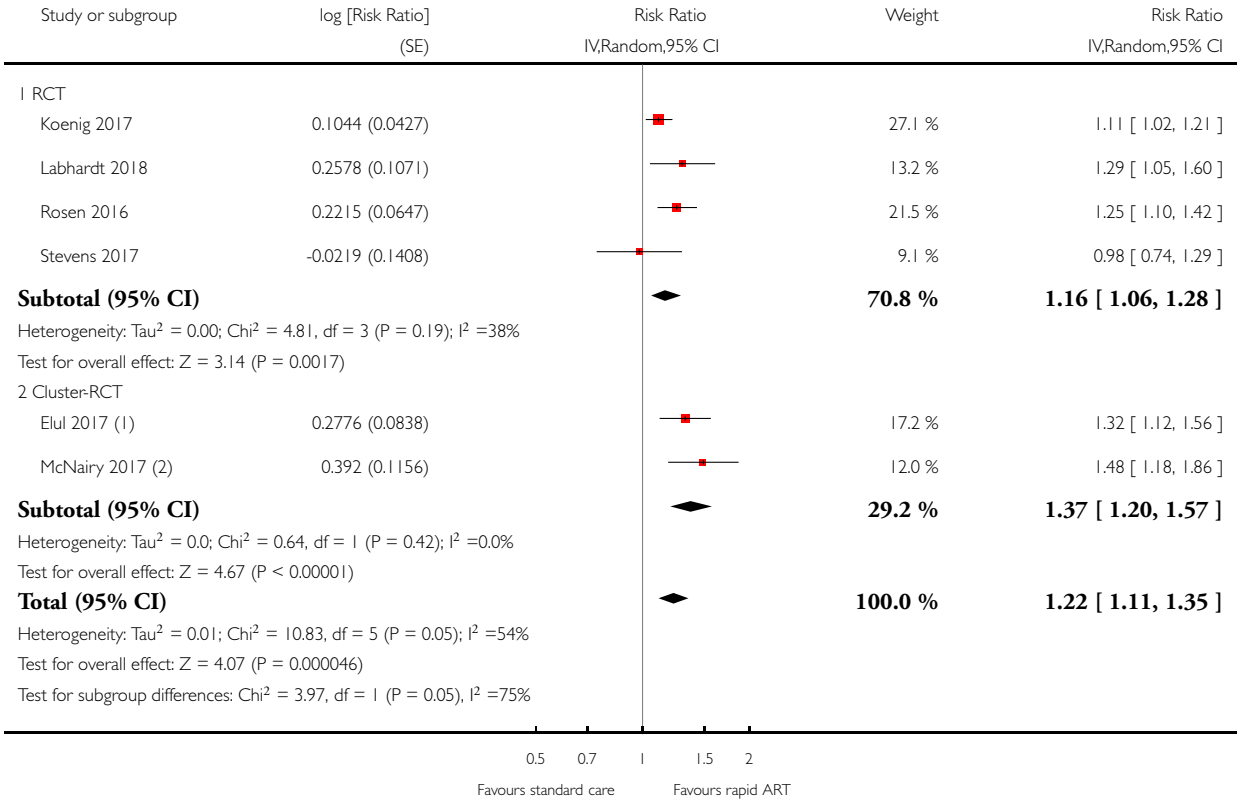


Analysis 1.3. Comparison 1 Rapid ART versus standard care, Outcome 3 Retention in care.

Review: Rapid initiation of antiretroviral therapy for people living with HIV

Comparison: 1 Rapid ART versus standard care

Outcome: 3 Retention in care



(1) CIS arm only

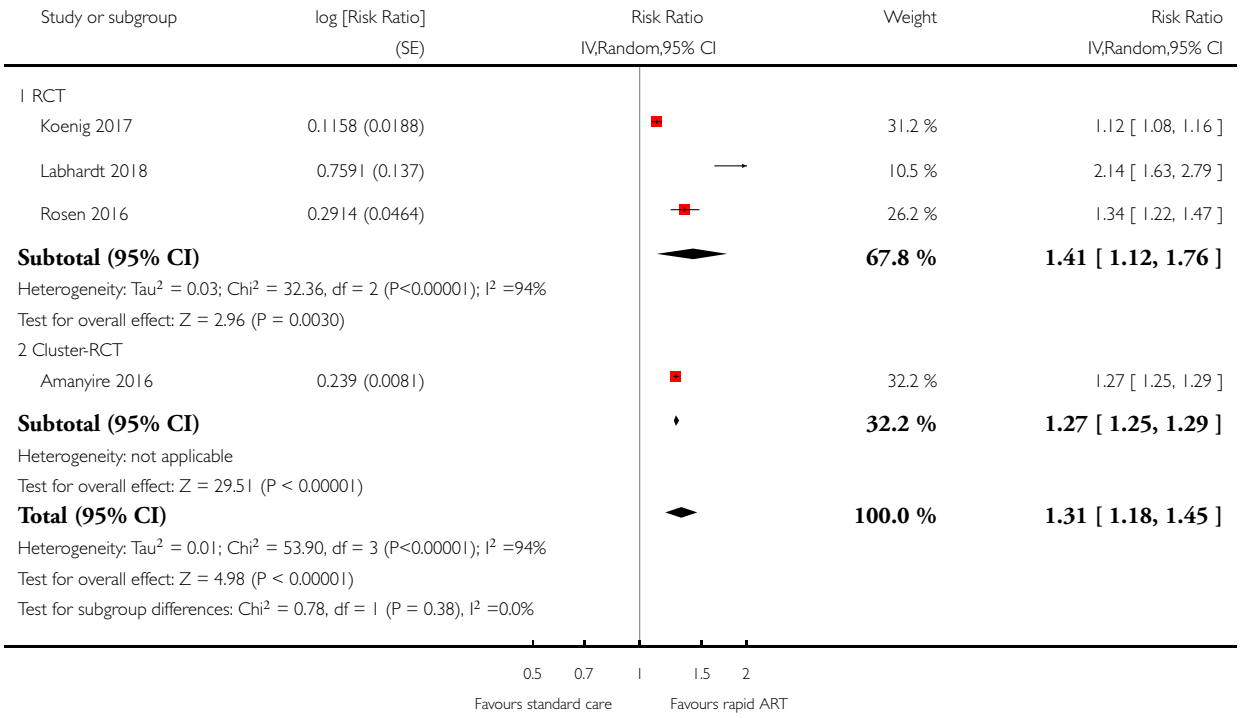
(2) Regardless of ART eligibility and uptake

Analysis 1.4. Comparison 1 Rapid ART versus standard care, Outcome 4 Uptake of ART at 90 days.

Review: Rapid initiation of antiretroviral therapy for people living with HIV

Comparison: 1 Rapid ART versus standard care

Outcome: 4 Uptake of ART at 90 days

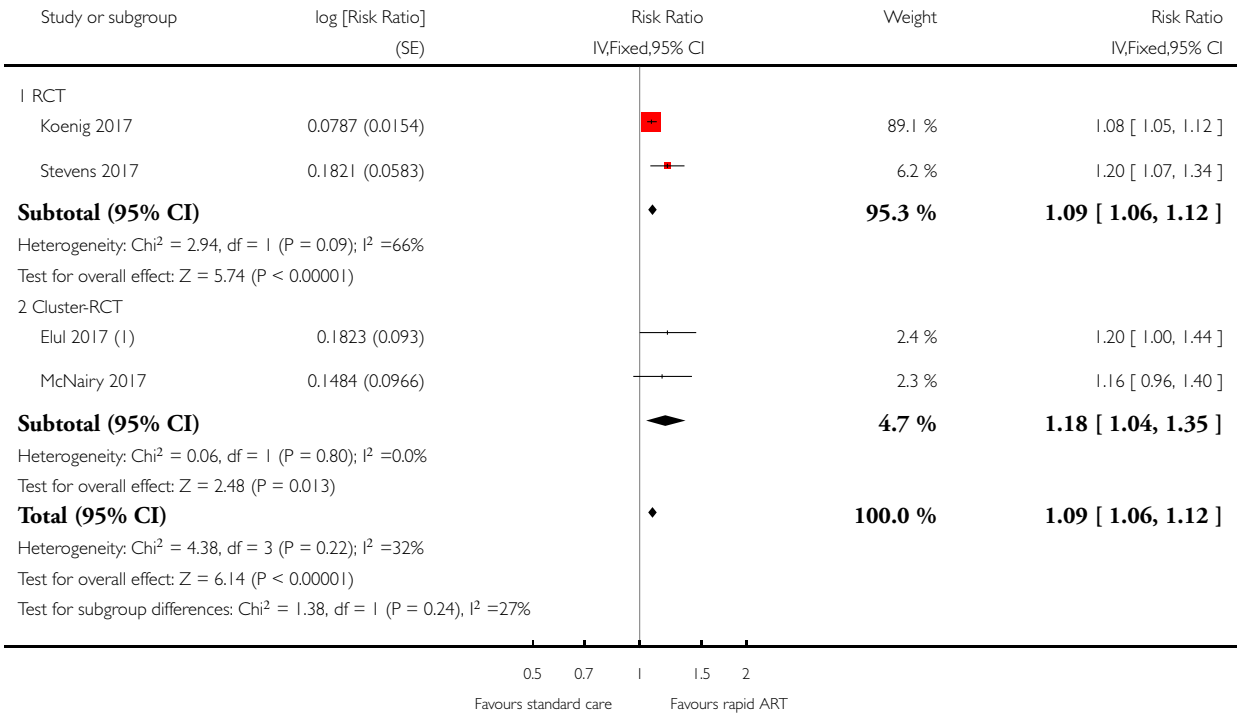


Analysis 1.5. Comparison 1 Rapid ART versus standard care, Outcome 5 Uptake of ART at 12 months.

Review: Rapid initiation of antiretroviral therapy for people living with HIV

Comparison: 1 Rapid ART versus standard care

Outcome: 5 Uptake of ART at 12 months



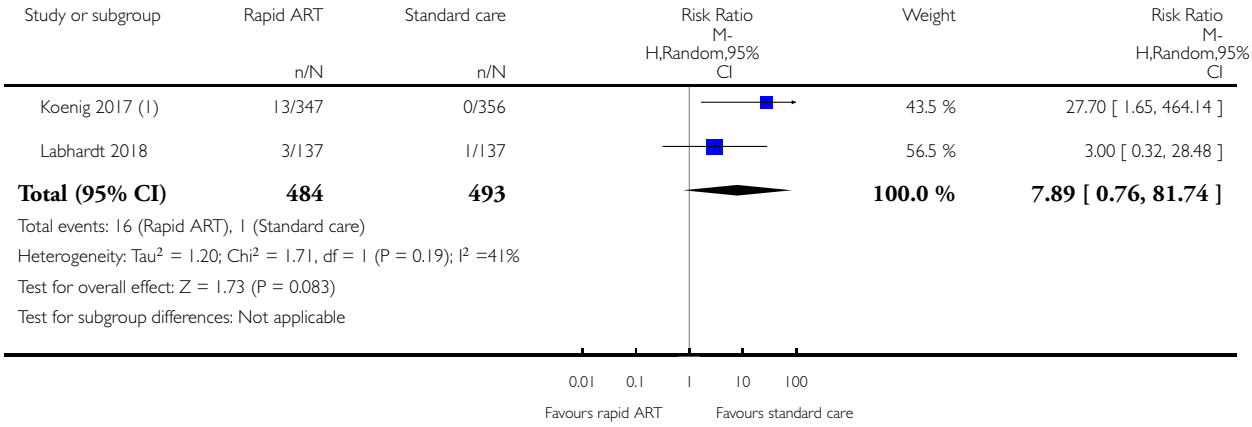
(1) CIS arm only

Analysis 1.6. Comparison 1 Rapid ART versus standard care, Outcome 6 Treatment modification.

Review: Rapid initiation of antiretroviral therapy for people living with HIV

Comparison: 1 Rapid ART versus standard care

Outcome: 6 Treatment modification



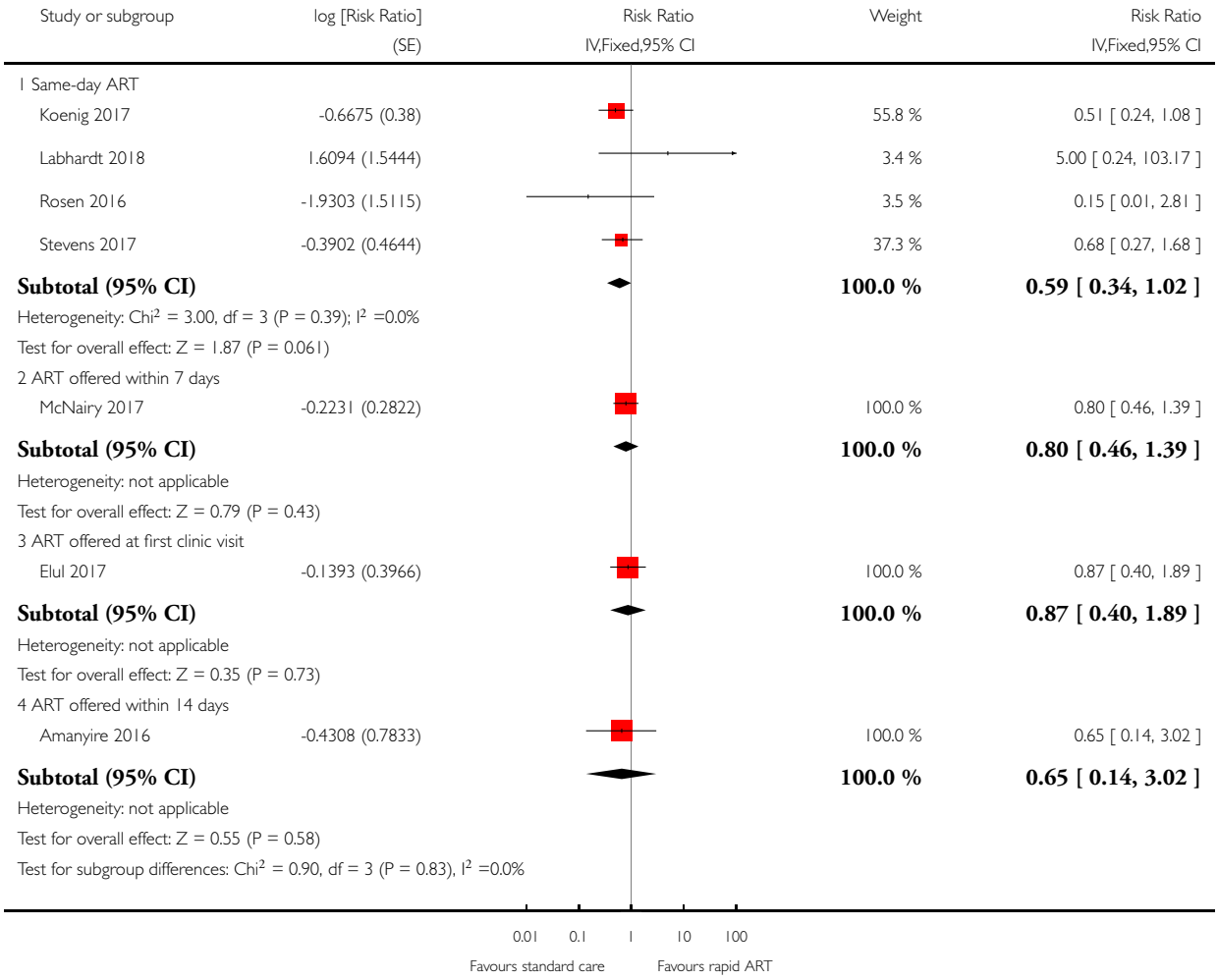
(1) No POCT U%Es available - changed regimen on day 3

Analysis 2.1. Comparison 2 Rapid ART versus standard care: subgroup analysis by time of ART initiation, Outcome 1 Mortality.

Review: Rapid initiation of antiretroviral therapy for people living with HIV

Comparison: 2 Rapid ART versus standard care: subgroup analysis by time of ART initiation

Outcome: 1 Mortality

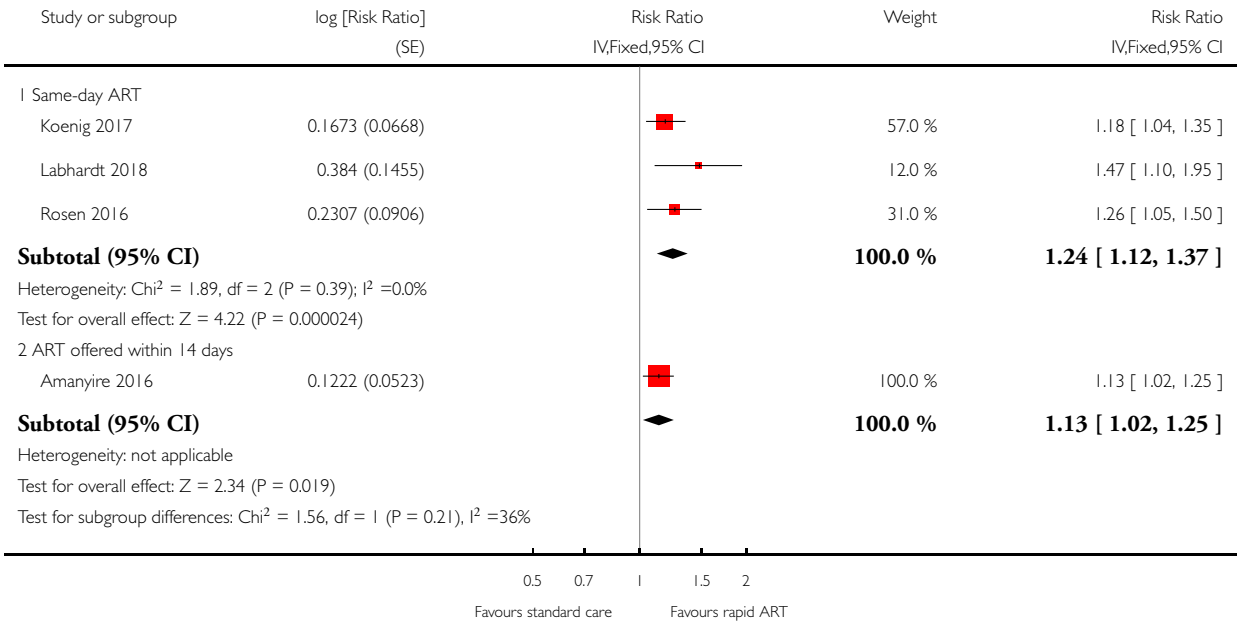


Analysis 2.2. Comparison 2 Rapid ART versus standard care: subgroup analysis by time of ART initiation, Outcome 2 Virological suppression at 12 months.

Review: Rapid initiation of antiretroviral therapy for people living with HIV

Comparison: 2 Rapid ART versus standard care: subgroup analysis by time of ART initiation

Outcome: 2 Virological suppression at 12 months

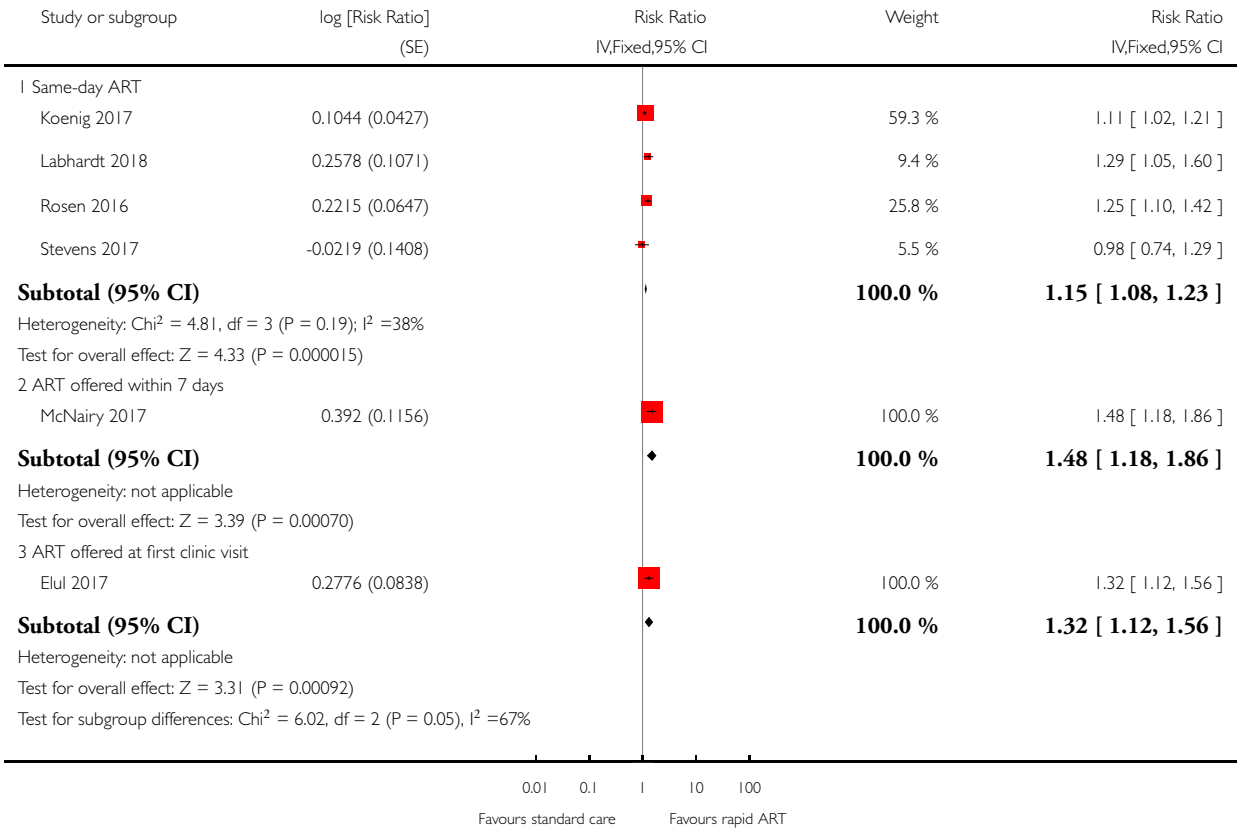


Analysis 2.3. Comparison 2 Rapid ART versus standard care: subgroup analysis by time of ART initiation, Outcome 3 Retention in care.

Review: Rapid initiation of antiretroviral therapy for people living with HIV

Comparison: 2 Rapid ART versus standard care: subgroup analysis by time of ART initiation

Outcome: 3 Retention in care

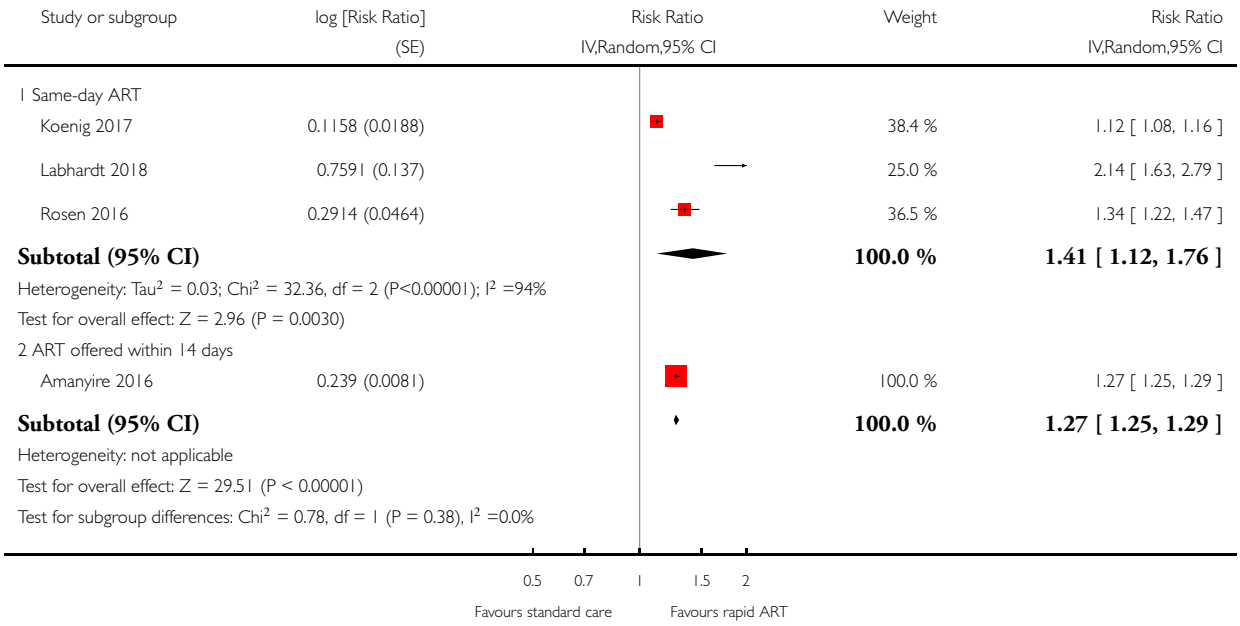


Analysis 2.4. Comparison 2 Rapid ART versus standard care: subgroup analysis by time of ART initiation, Outcome 4 Uptake of ART at 90 days.

Review: Rapid initiation of antiretroviral therapy for people living with HIV

Comparison: 2 Rapid ART versus standard care: subgroup analysis by time of ART initiation

Outcome: 4 Uptake of ART at 90 days

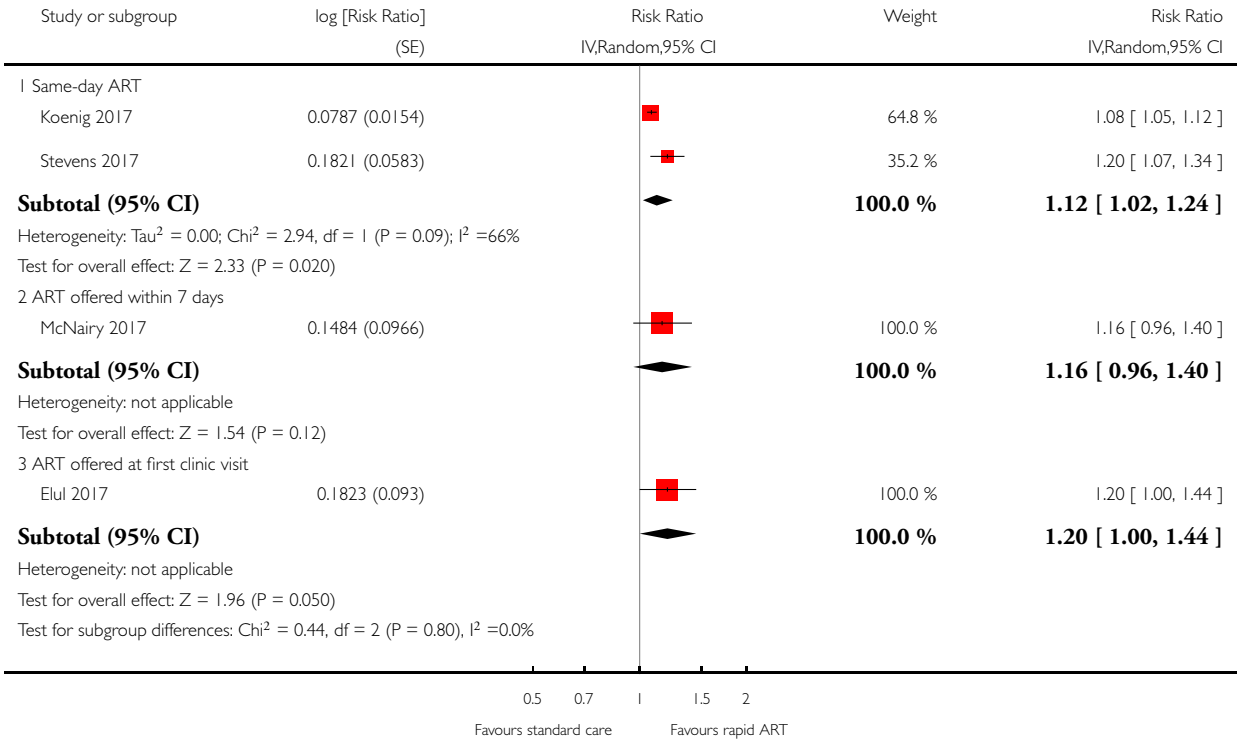


Analysis 2.5. Comparison 2 Rapid ART versus standard care: subgroup analysis by time of ART initiation, Outcome 5 Uptake of ART at 12 months.

Review: Rapid initiation of antiretroviral therapy for people living with HIV

Comparison: 2 Rapid ART versus standard care: subgroup analysis by time of ART initiation

Outcome: 5 Uptake of ART at 12 months

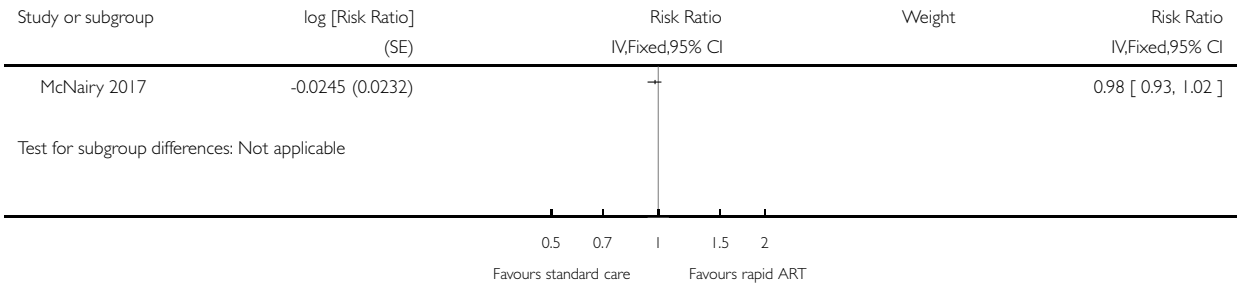


Analysis 3.1. Comparison 3 Rapid ART versus standard care, virological suppression: analysis by method of measurement, Outcome 1 Virological suppression at 12 months in participants on ART for at least 6 months.

Review: Rapid initiation of antiretroviral therapy for people living with HIV

Comparison: 3 Rapid ART versus standard care, virological suppression: analysis by method of measurement

Outcome: 1 Virological suppression at 12 months in participants on ART for at least 6 months



ADDITIONAL TABLES

Table 1. Antiretroviral treatment and prophylaxis for pregnant women according to the WHO Prevention of mother-to-child transmission programmes

Options	Treatment for pregnant women with CD4 count < 350 cells/mm³	Prophylaxis for pregnant women with CD4 count > 350 cells/mm³
Option A	ART started as soon as HIV is diagnosed, continued for life	Antivirals started as soon as 14 weeks of gestation and continued until 7 days post-partum
Option B	ART started as soon as HIV is diagnosed, continued for life	Antivirals started as soon as 14 weeks of gestation until childbirth if not breastfeeding or until one week after cessation of breastfeeding
Option B+	ART initiated as soon as HIV diagnosis and continued for life	

Source: WHO 2012.

Abbreviations: ART: antiretroviral therapy; WHO: World Health Organization.

Table 2. Interventions delivered alongside rapid antiretroviral therapy (ART) in the intervention arm

Study	Intervention target		
	Individual[a]	Health system[b]	
		Health-providers	Healthcare structures and processes
Amanyire 2016	• ART initiation within 14 days of eligibility • Individualized counselling including assessment of ART readiness	• Opinion-leader-led training of healthcare workers on the benefits of early ART, including lectures, introduction of revised 'less strict' counselling approach, and ART readiness assessment • Feedback on ART initiation rates	• POC HIV diagnosis and CD4 count • No need for treatment supporters • Flexible number of pre-ART counselling sessions
Elul 2017	• ART initiation at 1st visit after diagnosis • Counselling session on day of presentation • Mobile phone visit reminders • Non-cash FI[c,d]	• Receptionists expedited PLWH appointments • Clinicians encouraged to start ART on 1st clinic visit	• POC HIV diagnosis and CD4 count • Paper-based referral to on-site HIV services • 1st consultation within 1 week from diagnosis
Koenig 2017	• Same-day ART initiation • Readiness assessment survey[e] • 30-min adherence counselling • Participants received transport subsidies per visit	• Social worker: readiness assessment, adherence counselling • Physician: physical evaluation and adherence counselling • Pharmacist: dispense ART	• POC HIV diagnosis and CD4 count • No pre-ART clinic visits • 4 adherence counselling sessions and OI assessments within 17 days from presentation
Labhardt 2018	• Same-day ART initiation • Short adherence counselling • Leaflet with importance of adherence handed to participant • 30-day supply of ART if ready to start, assessed by study nurse	• POC tests, counselling, readiness assessment and ART dispensing performed by nurse on day of HIV diagnosis	• POC HIV diagnosis and CD4 count • No pre-ART clinic visits • Longer intervals between follow-up visits • Testing, diagnosis, counselling and ART dispensing at PLWH's home
McNairy 2017	• ART initiation within 1 week of testing • 2 pre-ART counselling sessions • Participant provided with health education package every 3 months[g] • Mobile phone visit reminders • Non-cash FI[c]	• Counsellors: conduct abbreviated counselling • HCWs: use checklist to determine readiness to initiate ART	• POC HIV diagnosis and CD4 count • Reduced number of pre-ART counselling sessions

Table 2. Interventions delivered alongside rapid antiretroviral therapy (ART) in the intervention arm (*Continued*)

Rosen 2016	• Same-day ART initiation • Adherence and counselling[f] on day of presentation • ARVs dispensed on 1st day	• Blood test, TB screening, physical examination, education, counselling and ARV dispensing by study nurse • Staff received study- and instrument-specific training	• POC HIV diagnosis and CD4 count • Rapid TB test • No-pre ART clinic visits
Stevens 2017	• Same-day ART • Same-day adherence counselling	• Staff received instrument-specific training	• POC CD4 testing and POC chemistry and haematology testing • No pre-ART visits

Abbreviations: ART: antiretroviral therapy; ARV: antiretroviral; FI: financial incentive; HCW: healthcare worker; OI: opportunistic infections; PLWH: people living with HIV; POC: point-of-care; TB: tuberculosis

[a] The aim of the intervention is to act on service users.

[b] The intervention, rather than acting on service users, acts on different parts of the healthcare system: health workers or the current health structures and processes.

[c] Prepaid mobile airtime.

[d] Only included in one of the two intervention groups (enhanced combined intervention strategy (CIS+)).

[e] Survey adapted from Balfour 2007.

[f] Counselling session included assessment of readiness to start ART.

[g] Including pillbox, condoms, toothbrush, and toothpaste.

Table 3. Main characteristics of included studies

Study	Group	Study type	Participants (N)	Median/ mean age (years)	Gender (% female)	Median/ mean CD4- (cells/mL)	Country and setting	Time to ART initiation	Relevant review outcomes reported
Amanyire 2016	I	Cluster-RCT	4747	30	60%	320	Uganda, urban + rural	80% within 14 days after diagnosis	Mortality Viral suppression Uptake of ART
	C		7277	31	65%	304		38% within 14 days after eligibility confirmed	
Elul 2017	I (CIS)	Cluster-RCT	557	35	66%	NR	Mozambique, urban + rural	Median time from diagnosis: 32 days	Mortality Retention in care at 12 months

Table 3. Main characteristics of included studies (*Continued*)

									Uptake of ART
	I (CIS+)		372	34	65%	NR			
	C		474	34	63%	NR		Median time from diagnosis: 63 days	
Koenig 2017	I	RCT	347	37	48%	249	Haiti, urban	99% day of diagnosis	Mortality Viral suppression Retention in care (12 to 15 months) Uptake of ART
	C		356	37	51%	NR		79% by 1 month after diagnosis	
Labhardt 2018	I	RCT	137	41	66%	346	Lesotho, rural	Planned on day of diagnosis	Mortality Viral suppression Retention in care (11 to 14 months) Treatment modification
	C		137	38	66%	417		Planned after 2nd ART visit	
McNairy 2017	I	Cluster-RCT	1096	32	60%	311	Swaziland (today known as eSwatini), urban + rural	Median time from diagnosis: 7 days	Mortality Viral suppression Retention in care at 12 months Uptake of ART
	C		1101	30	58%	285		Median time from diagnosis: 14 days	
Rosen 2016	I	RCT	187	> 18[a]	55%	224	South Africa, urban	72% started on enrolment day	Mortality Viral suppression Retention in care (5 to 10 months)

Table 3. Main characteristics of included studies (*Continued*)

	C		190	> 18[a]	58%	195		58% within 1 month after diagnosis	Uptake of ART
Stevens 2017	I	RCT	234	37.5	59.1%	200	South Africa, NR	Median from presentation: 1 days	Mortality Retention in care at 12 months Uptake of ART
	C		198	37.4	62.2%	165.7		Median from presentation 26.5 days	

Abbreviations: **I:** intervention; **C:** control; **ART:** antiretroviral therapy; **CIS:** combination intervention strategy; **CIS+:** enhanced combination intervention strategy; **d:** day; **N:** number; **NR:** not reported; **RCT:** randomized controlled trial

[a] Study did not report age; inclusion specified over 18 years.

Table 4. Summary of cohort studies investigating the effect of rapid antiretroviral therapy (ART)

Study	Country	Population (number of participants)	Intervention and comparison	Outcome					Summary
				Mortality	Viral suppression	Uptake	Retention	Adherence	
Langwenya 2018	South Africa	Pregnant women (628)	Same-day ART initiation versus delayed ART	N/A	Adjusted OR of viral suppression at delivery in same-day ART versus delayed ART: 0.78, (95% CI 0.43 to 1.43) P = 0.808	N/A	Adjusted OR of retention in care at 12 months postpartum in same-day ART versus delayed ART: 1.48, (95% CI 0.85 to 1.58)	N/A	Same-day ART makes little to no difference in retention or viral suppression compared to delayed ART in pregnant women

Table 4. Summary of cohort studies investigating the effect of rapid antiretroviral therapy (ART) (*Continued*)

Oladele 2018	Nigeria	An estimation of all PLWH in 14 local government areas (164,389)	Model A: same-day ART initiation in community Model B: Referral for same-day ART initiation at health facility	N/A	N/A	Model A intervention increased uptake from 216 ART initiations to 560; P < 0.001) No change over time in the Model B group	N/A	N/A	Increase in ART uptake when offered in the community compared to facility referral
Pilcher 2017	USA	Adults (86)	Same-day ART initiation versus delayed ART	N/A	Median time to viral suppression Same-day ART: 56 days. Delayed ART: 79 days. P = 0.009	ART uptake at 90 days Same-day ART: 39/39 (100%) Delayed ART: 36/47 (77%)	LTFU rate at 6 months Same-day ART: 11 (12%) Delayed ART: 7 (14.9%) P = 0.52	N/A	Same-day ART shows better uptake and faster viral suppression compared to delayed ART. No differences in retention at 6 months
Ssebunya 2017	Uganda	Children (367)	ART initiation within 7 days of enrolment versus ART initiation > 7 days after enrolment	At 5 years: 15 deaths (8.3%) in early ART group versus 27 (14.4%) in delayed group P = 0.026	Median time to viral suppression = 24.9 months (95% CI 19.7 to 28.5 months) in early ART group versus 38.3 months (95%CI 31.1 to 44.5 months) in delayed group	N/A	At 5 years: LTFU = 6 (3.3%) in early ART group versus 16 (8.6%) in delayed initiation group	Adherence rate = 65 (36.1%) in early ART group versus 45 (34.2%) in delayed group	Initiating ART within 7 d was associated with lower mortality; better retention; faster viral suppression and possibly better adherence than initiating ART > 7 d after enrolment

Table 4. Summary of cohort studies investigating the effect of rapid antiretroviral therapy (ART) (*Continued*)

Vogt 2017	Zimbabwe	Adolescents aged ≥ 10 to < 19 years (1499)	Compared ART initiation between 7 and 14 d after diagnosis with ART initiation within: 0-7 d; 14-1 months; 1-2 months; ≥ 2 months after diagnosis	Adjusted HR of mortality at 24 months ART initiation 0-7 d versus 7-14 d after diagnosis: 1.59, 95% CI (0.83 to 3.04)	N/A	N/A	Adjusted HR of retention at 24 months ART initiation 0-7 days versus 7-14 days after diagnosis: 1.02 (95% CI 0.62 to 1.67)	N/A	Initiating ART within 7 d after diagnosis showed no difference in mortality or retention in care compared to initiating ART between 7-14 d after diagnosis
Zhao 2018	China	Adults (34,581)	Immediate ART: ART initiation within 30 d of eligibility Delayed ART: ART initiation > 30 d after eligibility No ART: no ART initiation	HR of mortality: Immediate ART versus no ART: 0.37, (95% CI 0.23 to 0.58) ; Delayed ART versus no ART: 0.74, (95% CI 0.57 to 0.98)	N/A	N/A	N/A	N/A	Immediate ART showed a stronger reduction in mortality compared to delayed ART

Abbreviations: ART: antiretroviral therapy; HR: hazard ratio; LTFU: loss to follow-up; N/A: not applicable; OR: odds ratio.

APPENDICES

Appendix 1. Search strategies

MEDLINE (PubMed)

Search	Query
#11	Search #5 AND #8 AND #9 AND #10
#10	Search #3 OR #4
#9	Search #1 OR #2
#8	Search #6 NOT #7
#7	Search animals [Mesh] NOT humans [Mesh]
#6	Search ((((((randomized controlled trial [pt]) OR controlled clinical trial [pt]) OR randomized [tiab]) OR placebo [tiab]) OR clinical trials as topic [mesh: noexp] OR randomly [tiab]) OR trial [tiab])
#5	Search Immediate OR rapid OR same-day OR "same day" OR fast-track OR "fast track" OR universal OR "test and treat" OR early OR accelerat* OR instant OR prompt OR fast OR quick OR expedit*
#4	Search antiretroviral agents [Mesh] OR antiretroviral therapy, highly active [Mesh]
#3	Search Antiretroviral* OR ((anti) AND (retroviral*)) OR ARV* OR ART OR "antiretroviral therapy" OR HAART OR ((highly) AND (active) AND (antiretroviral*) AND (therap*)) OR ((anti) AND (hiv)) OR ((anti) AND (acquired immunodeficiency)) OR ((anti) AND (acquired immuno-deficiency)) OR ((anti) AND (acquired immune-deficiency)) OR ((anti) AND (acquired immun*) AND (deficienc*))
#2	Search HIV infections [MeSH] OR HIV [MeSH]
#1	Search HIV OR hiv-1 OR hiv-2* OR hiv1 OR hiv2 OR hiv infect* OR human immunodeficiency virus OR human immune deficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus OR ((human immun*) AND (deficiency virus)) OR acquired immunodeficiency syndromes OR acquired immune deficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR ((acquired immun*) AND (deficiency syndrome)) OR HIV/AIDS

Embase (Ovid)

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1 *Human immunodeficiency virus/
2 *Human immunodeficiency virus infection/
3 (human immunodeficiency virus or human immune deficiency virus or human immuno-deficiency virus or human immune-deficiency virus).ab.
4 (human immunodeficiency virus or human immune deficiency virus or human immuno-deficiency virus or human immune-deficiency virus).ti.

5 (hiv-1* or hiv-2* or hiv1 or hiv2).ti. or (hiv-1* or hiv-2* or hiv1 or hiv2).ab.
6 (HIV or HIV AIDS).ti. or (HIV or HIV AIDS).ab.
7 (acquired immunodeficiency syndromes or acquired immune deficiency syndrome or acquired immuno-deficiency syndrome or acquired immune-deficiency syndrome).ti. or (acquired immunodeficiency syndromes or acquired immune deficiency syndrome or acquired immuno-deficiency syndrome or acquired immune-deficiency syndrome).ab.
8 (acquired immun* and deficiency syndrome).ti. or (acquired immun* and deficiency syndrome).ab.
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10 *antiretrovirus agent/
11 *highly active antiretroviral therapy/
12 (ARV* or ART or "antiretroviral therapy" or HAART or (highly and active and antiretroviral* and therap*)).ti. or (ARV* or ART or "antiretroviral therapy" or HAART or (highly and active and antiretroviral* and therap*)).ab.
13 ((highly and active and antiretroviral* and therapy) or (highly and active and antiretroviral* and therapeutic)).ti. or ((highly and active and antiretroviral* and therapy) or (highly and active and antiretroviral* and therapeutic)).ab.
14 ((anti and hiv) or (anti and acquired immunodeficiency)).ti. or ((anti and hiv) or (anti and acquired immunodeficiency)).ab.
15 ((anti and acquired immuno-deficiency) or (anti and acquired immune-deficiency) or (anti and acquired immun* and deficienc*)).ti. or ((anti and acquired immuno-deficiency) or (anti and acquired immune-deficiency) or (anti and acquired immun* and deficienc*)).ab.
16 10 or 11 or 12 or 13 or 14 or 15
17 9 and 16
18 (immediate or rapid or same-day or "same day" or fast-track or "fast track" or universal or "test and treat" or early or accelerat* or instant or prompt or fast or quick or expedit*).ti. or (immediate or rapid or same-day or "same day" or fast-track or "fast track" or universal or "test and treat" or early or accelerat* or instant or prompt or fast or quick or expedit*).ab.
19 17 and 18
20 random*.ti. or random*.ab.
21 placebo.ti. or placebo.ab.
22 (double-blind or "double blind").ti. or (double-blind or "double blind").ab.
23 randomized controlled trial/
24 *controlled clinical trial/
25 20 or 21 or 22 or 23 or 24
26 19 and 25

Web of Science - Core Collection

Science Citation Index Expanded (SCI-EXPANDED) --1970-present
Social Sciences Citation Index (SSCI) --1970-present
Conference Proceedings Citation Index- Science (CPCI-S) --1990-present

# 7	#6 AND #5 *Indexes=SCI-EXPANDED, SSCI, CPCI-S Timespan=All years*
# 6	**TITLE:** ("randomized controlled trial" OR "randomised controlled trial" OR "controlled clinical trial" OR random* OR placebo OR double-blind OR "double blind" OR single-blind OR "single blind") *Indexes=SCI-EXPANDED, SSCI, CPCI-S Timespan=All years*
# 5	#4 AND #3 *Indexes=SCI-EXPANDED, SSCI, CPCI-S Timespan=All years*
# 4	**TOPIC:** (Immediate OR rapid OR same-day OR "same day" OR fast-track OR "fast track" OR universal OR "test and treat" OR early OR accelerat* OR instant OR prompt OR fast OR quick OR expedit*) *Indexes=SCI-EXPANDED, SSCI, CPCI-S Timespan=All years*

(*Continued*)

# 3	#2 AND #1 *Indexes=SCI-EXPANDED, SSCI, CPCI-S Timespan=All years*
# 2	**TOPIC:** (antiretroviral OR ART OR HAART OR "highly active antiretroviral*" OR ARV) *Indexes=SCI-EXPANDED, SSCI, CPCI-S Timespan=All years*
# 1	**TOPIC:** (HIV* OR "HIV infect*" OR "human immunodeficiency virus") *OR* **TOPIC:** (AIDS OR HIV/AIDS OR "acquired immunodeficiency") *Indexes=SCI-EXPANDED, SSCI, CPCI-S Timespan=All years*

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#1 HIV or hiv-1 or hiv-2* or hiv1 or hiv2 or hiv infect* or human immunodeficiency virus or human immune deficiency virus or human immuno-deficiency virus or human immune-deficiency virus:ti,ab,kw (Word variations have been searched)
#2 (human immun*) and (deficiency virus) or acquired immunodeficiency syndromes or acquired immune deficiency syndrome or acquired immuno-deficiency syndrome or acquired immune-deficiency syndrome:ti,ab,kw (Word variations have been searched)
#3 acquired immun* and deficiency syndrome
#4 "HIV/AIDS"
#5 MeSH descriptor: [HIV] explode all trees
#6 MeSH descriptor: [HIV Infections] explode all trees
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 MeSH descriptor: [Anti-Retroviral Agents] explode all trees
#9 MeSH descriptor: [Antiretroviral Therapy, Highly Active] explode all trees
#10 antiretroviral*
#11 anti and retroviral*
#12 ARV* or ART or "antiretroviral therapy" or HAART
#13 highly and active and antiretroviral* and therap*
#14 anti and hiv
#15 anti and "acquired immunodeficiency"
#16 anti and "acquired immuno-deficiency"
#17 anti and "acquired immune-deficiency"
#18 anti and "acquired immun*" and deficienc*
#19 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
#20 #7 and #19
#21 Immediate or rapid or same-day or "same day" or fast-track or "fast track" or universal or "test and treat" or early or accelerat* or instant or prompt or fast or quick or expedit*:ti,ab,kw (Word variations have been searched)
#22 #20 and #21

LILACS

Search on :	**antiretroviral$ OR ART OR ARV OR HAART [Words] and rapid OR accelerat$ OR early OR fast OR immediate [Words] and random$ OR trial OR blind$ OR control$ OR compar$ [Words]**

Africa wide via Ebscohost 1990 to 2018

AB (antiretroviral* OR ART OR ARV OR HAART) AND TI (rapid OR accelerate* OR fast OR immediate OR early) AND (random* OR trial OR control* OR blind*) AND AB (HIV* OR HIV/AIDS OR AIDS)

ClinicalTrials.gov

rapid OR early OR immediate OR accelerate OR fast | Interventional Studies | antiretroviral OR ART OR ARV OR HAART

WHO ICTRP

Title: (rapid OR early OR immediate OR accelerate OR fast) AND
Condition: (HIV OR HIV/AIDS) AND
Intervention: (antiretroviral OR ART OR ARV OR HAART)
Recruitment status: All

Appendix 2. Study eligibility form

Review title or ID					
Study ID					
Report ID					
Date form completed (dd/mm/yyyy)					
Study characteristics	**Eligibility criteria**	**Eligibility criteria met?**			**Location in text or source (page and paragraph/fig/table/other)**
		Yes	**No**	**Unclear**	
Type of study	Randomized controlled trial or cluster-randomized trial				
Participants	HIV positive adults, adolescents, children or pregnant women taking antiretroviral ther-				

(*Continued*)

	apy (ART) for their own health				
Types of intervention	Rapid ART (defined as receiving antiretroviral therapy within 7 days of HIV diagnosis) plus usual care (for example, counselling, opportunistic infection screening)				
Types of comparison	Delayed ART (defined as receiving antiretroviral therapy at any time after 7 days post-HIV diagnosis) plus usual care				
Types of outcome measures	Viral suppression at 12 months and/or rentention in care at 12 months and/or uptake of ART and/or incidence of IRIS and/or incidence of regimen change				
INCLUDE (Yes/No):	EXCLUDE (Yes/No):				
Reason for exclusion					
Notes:					

CONTRIBUTIONS OF AUTHORS

AMU, RS, IEW, and SJ screened studies, extracted data, analysed results, and contributed to the writing of the review.

JBN contributed to the design of the review, provided input on analysis and interpretation of the results, and contributed to writing the review.

All review authors responded to the referee comments and approved the final review version.

DECLARATIONS OF INTEREST

AMU has no known conflicts of interest.

SJ has no known conflicts of interest.

RS has no known conflicts of interest.

JBN has no known conflicts of interest.

IEW has no known conflicts of interest.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We defined rapid ART as offering ART to people living with HIV within seven days of diagnosis. In our review, however, we included a study that aimed to offer ART within 14 days of diagnosis (Amanyire 2016). We performed a subgroup analysis to examine the effects of starting ART within seven days compared with 14 days.

We did not specify in the protocol, but we also excluded studies that offered ART in the context of pre-exposure or post-exposure prophylaxis.

During the review process, we identified significant variation in study design; as such we conducted a subgroup analysis to examine the effect of cluster-designed RCTs.

In the protocol we stated that, to measure retention in care at 12 months, we would use results within the range of 6 to 14 months. However, we also included data from a study that reported retention in care between 5 and 10 months (Rosen 2016), because it was not possible to differentiate which participants fell into the 6- to 10-month range.

RS joined the review author team.