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Received: 11 August 2021 | Accepted: 13 August 2021

DOI: 10.1111/hiv.13169

REVIEW ARTICLE

Same-day antiretroviral therapy initiation for people living with HIV who have tuberculosis symptoms: a systematic review

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Funding information
This work was supported by a grant from WHO Global HIV, Hepatitis and STIs Programme. Further details of funding of individual authors is detailed in the Acknowledgements.

Abstract

Objectives: Tuberculosis symptoms are very common among people living with HIV (PLHIV) initiating antiretroviral therapy (ART), are not specific for tuberculosis disease and may result in delayed ART start. The risks and benefits of same-day ART initiation in PLHIV with tuberculosis symptoms are unknown.

Methods: We systematically reviewed nine databases on 12 March 2020 to identify studies that investigated same-day ART initiation among PLHIV with tuberculosis symptoms and reported both their approach to TB screening and clinical outcomes. We extracted and summarized data about TB screening, numbers of people starting same-day ART and outcomes.

Results: We included four studies. Two studies deferred ART for everyone with any tuberculosis symptoms (one or more of cough, fever, night sweats or weight loss) and substantial numbers of people had deferred ART start (28% and 39% did

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not start same-day ART). Two studies permitted some people with tuberculosis symptoms to start same-day ART, and fewer people deferred ART (2% and 16% did not start same-day). Two of the four studies were conducted sequentially; proven viral load suppression at 8 months was 31% when everyone with tuberculosis symptoms had ART deferred, and 44% when the algorithm was changed so that some people with tuberculosis symptoms could start same-day ART.

Conclusions: Although tuberculosis symptoms are very common in people starting ART, there is insufficient evidence about whether presence of tuberculosis symptoms should lead to ART start being deferred or not. Research to inform clear guidelines would help to maximise the benefits of same-day ART.

KEYWORDS

guidelines, HIV, same-day ART, tuberculosis, tuberculosis screening

INTRODUCTION

People living with HIV (PLHIV) require antiretroviral therapy (ART) as part of comprehensive HIV care services. Antiretroviral therapy should be started as soon as possible after the first positive HIV diagnosis, or after re-engagement in clinical care [1-3]. Tuberculosis (TB) is common in PLHIV and is a particularly important cause of early mortality following HIV diagnosis [4,5]. Screening, treatment and prevention of TB are key interventions for reducing mortality and morbidity for individuals, as well as reducing community TB transmission.

Same-day ART (ART started on the same day as first presentation to HIV services) has been shown to reduce pre-treatment loss to follow-up and was recommended by WHO in their 2017 *Guidelines for Managing Advanced HIV Disease and Rapid Initiation of Antiretroviral Therapy* [3]. That 2017 guideline stated as a 'clinical consideration' that for people with TB symptoms, ART should be 'briefly' delayed whilst investigating for TB – this clinical consideration was amended in March 2021 guidelines to suggest that ART could be started in people with TB symptoms (excluding headache or other neurological symptoms) with 'close follow up within 7 days' [6]. Tuberculosis symptoms are defined as any one of more of fever, cough of any duration, night sweats or weight loss. This rationale to delay ART to investigate for TB is primarily due to concerns of immune reconstitution inflammatory syndrome (IRIS) occurring in people with undiagnosed and untreated TB at the time of ART initiation [7]. However, TB symptoms are very common among PLHIV not yet on ART – 71% prevalence in a systematic review [7] – and are not specific for TB. It can be difficult to either diagnose TB or confidently refute the diagnosis, particularly at a single clinic visit or in a single day. While in theory, sputum testing for TB using nucleic acid amplification tests (NAATs, such as Xpert Mtb/Rif) can be performed in 2 h, in practice NAAT machines are often located off-site and may have testing backlogs; therefore same-day results are usually not available. Furthermore a single negative sputum NAAT does not exclude TB, and some people are unable to produce sputum. If all people with TB symptoms requiring ART initiation had ART initiation deferred, then a large number of people may not be able to access the benefits of same-day ART. Figure 1 summarizes how TB screening to determine same-day ART eligibility might lead to benefits or harms for individuals.

We undertook a systematic review to synthesize the evidence on the risks and benefits of same-day ART initiation in PLHIV, not already on ART and with TB symptoms. Because there were very few studies that addressed this question directly by describing their TB screening algorithm, we additionally undertook a narrative review of all identified studies of same-day ART initiation, regardless of whether or how TB screening was reported, in order to make recommendations for further research priorities.

METHODS

Inclusion and exclusion criteria

Ideally we sought trials which recruited a group of people being assessed for same-day ART, and directly compared those allocated to one TB screening algorithm or approach with those allocated to another, with reported outcomes in both groups. However, at scoping stage, no study making this direct comparison was identified. Therefore we included studies that recruited a group of PLHIV at the point of first presentation for ART and where there was an intention to start at least some people on same-day ART (i.e. those who were 'eligible' for same-day ART would

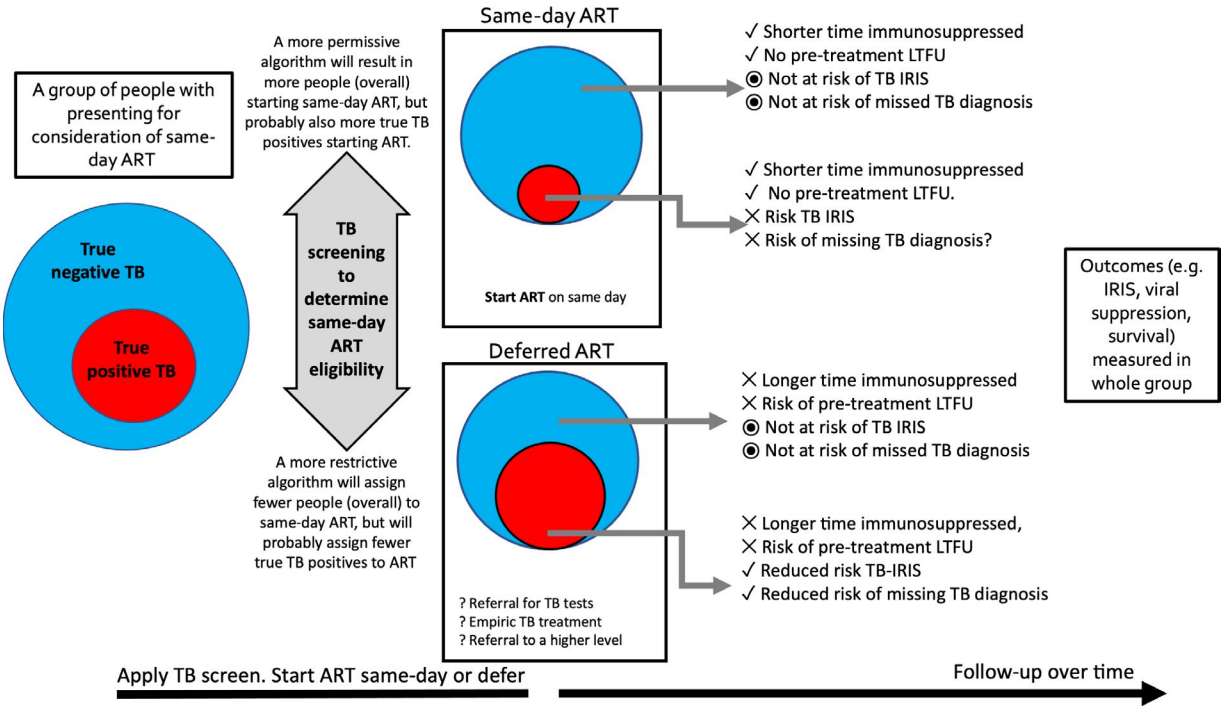


FIGURE 1 Schema of how an intervention to screen for tuberculosis (TB) to determine same-day antiretroviral therapy (ART) eligibility might lead to participant harms or benefits. IRIS, immune reconstitution inflammatory syndrome; LTFU, loss to follow-up. Ticks represent possible benefits and crosses possible harms

start) and where TB screening procedures and how these affected eligibility for same-day ART were described. The TB screen could take any form (i.e. symptoms or symptoms and same-day tests).

We included studies that reported one or more of the following outcomes of interest: time to ART initiation; ART retention; viral load suppression; serious adverse events; IRIS events; or mortality. Studies could be in any country and among adults or children. We excluded studies where participants were 'pre-screened' for TB before enrolling in study, or where outcomes were only reported for the subset of participants who actually started ART (i.e. that excluded outcomes for people with pre-treatment loss to follow-up). We also excluded studies that reported on same-day ART only in the context of people with acute HIV or neonates undergoing early infant diagnosis of HIV. There was no requirement for studies to have a comparison group and single arms of multi-arm trials could be included. As a secondary objective, because so few studies reported TB screening details, we identified all observational studies of same-day ART regardless of whether TB screening details or outcomes of interest were described.

Search strategy

On 12 March 2020 we searched the following databases using terms around ART and same-day or rapid initiation: Ebsco Africa-Wide Information; Ebsco CINAHL Plus; Wiley Cochrane Central Register of Controlled Trials; OvidSP Embase; OvidSP Global Health; World Health Organization Global Index Medicus; OvidSP Medline; and Clarivate Analytics Web of Science. We included papers published from 1 January 2003, as 2003 was the year ART began to become widely available to PLHIV in low-resource settings. We also searched clinical trials registers: Clinical Trials.gov and World Health Organization International Clinical Trials Registry Platform on 12 March 2020. The search strategy is available at PROSPERO (CRD42020205490,

https://www.crd.york.ac.uk/PROSPEROFILES/205490_PROTOCOL_20200822.pdf).

Titles and abstracts were screened by RMB and HMR. After reviewing 10% in duplicate and determining perfect agreement, the remainder were screened by one person only. Where full text review was required, RMB and HMR reviewed in duplicate. Inclusion decisions were made by consensus and discussion with PM and RJW. We searched reference lists from selected manuscripts to identify any additional relevant studies.

Data extraction and synthesis

Data of study characteristics (country, population, details of TB screening, other eligibility criteria for same-day

ART) and outcomes (as described above) were extracted by RMB and HR from included studies into a spreadsheet in duplicate and discrepancies were reconciled by consensus. We contacted authors of papers where we thought there might be relevant information not included in the published paper. We synthesized data in narrative summary form. Where appropriate, we used Cochrane ROBINS-I tool to assess bias [8].

RESULTS

The database search returned 5372 non-duplicate articles. We reviewed 186 full-text articles (Figure 2) and included four studies (six articles). A further 27 studies (30 articles) were identified which contained some data on people who started same-day ART but not full details of TB screening algorithm or participant outcomes.

We did not identify any studies that directly compared two or more approaches to determining eligibility for same-day ART based on TB screening. We identified four eligible studies where a TB screening algorithm was used to determine eligibility for same-day ART, all of which were trials of same-day ART versus standard care. We only included data from the intervention arm of each trial as people in the standard care arm were not being assessed for same-day ART. Table 1 shows detailed descriptions of these studies and outcomes.

RapIT [9] was a trial of expedited ART initiation at primary care clinics in South Africa. PLHIV with CD4 cell count <350 cells/μL were permitted to start same-day ART if they had none of the four WHO TB symptoms. People with TB symptoms were asked to submit sputum for Xpert and could start ART if Xpert-negative (in effect, meaning not on the same day as first presentation for most people), or two weeks after TB treatment initiation if Xpert positive. CASCADE was a trial of home-based HIV testing and same-day ART initiation in Lesotho [10]. People newly diagnosed with HIV could start ART on the same day as their HIV test regardless of TB symptoms. Participants were asked about TB symptoms and anyone with one or more of four WHO TB symptoms was asked to provide sputum for Xpert testing, but was permitted to start ART without waiting for the result. In SLATE I,

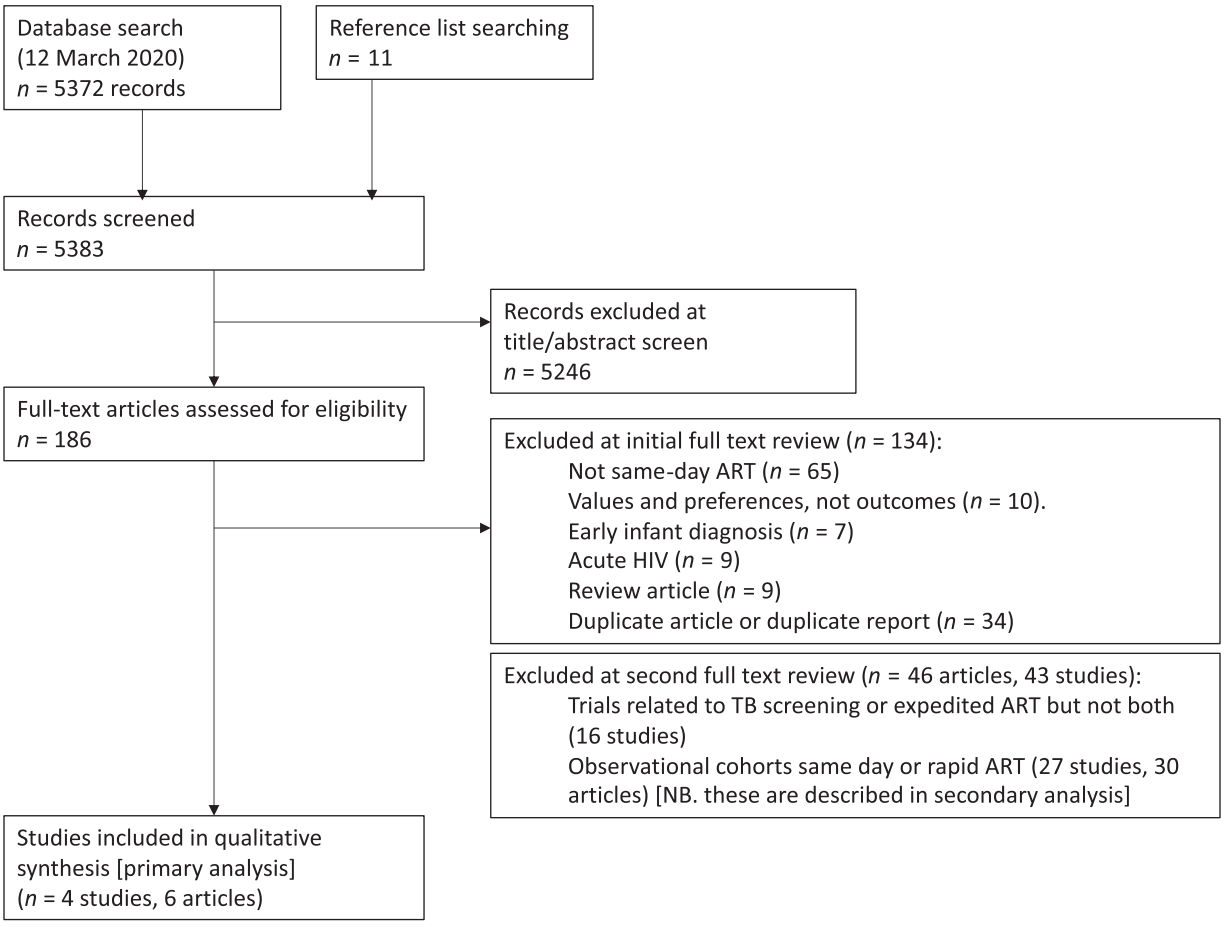


FIGURE 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram

TABLE 1 Characteristics of included studies

	Study			
Parameter	**Rosen et al. [9] (RAPiT)**	**Labhardt et al. [10] (CASCADE)**	**Rosen et al. [11] (SLATE I)**	**Maskew et al. [12] (SLATE II)**
Country/setting/dates	Two public-sector clinics in South Africa, May 2013 to August 2014	60 rural villages and 17 urban areas in Lesotho, February 2016 to Sept 2017	Three primary care clinics in South Africa and two in Kenya, March 2017 to April 2018	Three primary care clinics in South Africa, March to September 2018
Population	Adults (≥ 18 years), not pregnant, not currently on ART, CD4 count < 350 cells/μL; presented to clinic to start ART or received first positive HIV test	Adults (≥ 18 years), not pregnant, HIV-positive during community-based HIV testing, not currently on ART	Adults (≥ 18 years), not pregnant, not currently on ART; presented to clinic to start ART or received first positive HIV test	Adults (≥ 18 years), not pregnant, not currently on ART; presented to clinic to start ART or received first positive HIV test
No. and demographics of people recruited	187 people in SDART arm, mITT population Female: 129/234 (55%) Median (IQR) age: 34 (29–40) years Median (IQR) CD4 count: 224 (128–327) cells/μL	137 people in same-day ART arm, mITT population Female: 90/137 (66%) Median (IQR) age: 41 (31–53) years Median (IQR) CD4 count: 346 (244–497) cells/μL	538 randomized to SLATE algorithm arm (298 in South Africa, 240 in Kenya) Female: 331/538 (62%) Median (IQR) age (years): South Africa, 34 (29–41); Kenya, 36 (29–44) Median (IQR) CD4 count: South Africa, 275 (132–459) cells/μL; Kenya, 272 (124–522) cells/μL	296 in SLATE II algorithm arm. Female: 189/296 (64%) Median (IQR) age: 35 (29–41) years Median (IQR) CD4 count: 298 (137–482) cells/μL
Same-day ART intervention	Point of care CD4, same-day education/counselling about ART and same-day initiation if CD4 < 350 cells/μL	Post-test HIV counselling and ART counselling. 30 day ART supply given to participants at their house, ART refills then at health facilities	Same-day ART offered to all those who met the criteria as specified in the SLATE algorithm (see below). Referral back to usual care if not eligible for same-day ART according to SLATE algorithm	Same-day ART offered to all those who met the criteria specified in SLATE II algorithm (see below). Referral back to usual care if not eligible for same-day ART according to SLATE II

(Continues)

TABLE 1 (Continued)

Parameter	Study Rosen et al. [9] (RAPiT)	Labhardt et al. [10] (CASCADE)	Rosen et al. [11] (SLATE I)	Maskew et al. [12] (SLATE II)
Eligibility for same-day ART	• CD4 < 350 cells/μL or a WHO stage 3/4 clinical condition • Does not require off-site referral for 'assessment of specific medical conditions' • No TB symptoms or TB symptoms and a negative sputum Xpert (in effect, as Xpert results took some time to come back, those with TB symptoms were unlikely to be able to start on same day)	• 'Ready' to start ARTNB: Note that eligibility criteria to be in the trial in the first place excludes people with 'clinical WHO stage 4 condition' or 'in care for another chronic medical condition'. People with one or more TB symptom were asked to provide sputum for TB testing, but could start ART without awaiting result	• No TB symptoms (if TB symptoms, referred back to usual care for assessment and ART initiation) • No prior ART and no concurrent medications • No concerning features on physical exam • 'Ready' to start ART	• No 'severe' TB symptoms and urine LAM test negative • No persistent headache or 'serious self-reported symptoms' • Never had ART stopped due to side effects or allergy and no concomitant medications • No concerning features on physical exam • 'Ready' to start ARTAll were asked for sputum for Xpert testing, but could start ART without awaiting the result
Algorithm results				
TB symptoms	29/187 (16%)	2/137 (1.5%)	202/538 (38%) 109 /298 (37%) – South Africa 93/240 (39%) – Kenya	140/296 (47%)
Ineligible to start same-day ART (for any reason)	30 /187 (16%)	3/137 (2%)	258 /538 (48%) 149/298 (50%) – South Africa 109/131 (45%) – Kenya	41/296 (14%)
Ineligible for same-day ART at least in part because of TB symptoms	Unknown	0/137 (0%)	202/538 (38%)	39/538 (7%)
TB outcomes				
No. diagnosed with TB (microbiologically confirmed or empirical treatment) as a result of investigations at enrolment	4/187 (2%)	0/137 (0%)	21/538 (4%)	7/296 (2%)
No. diagnosed with incident TB during follow-up	Unknown	0 /137 (0%)	1/538 (0.19%, passive record review)	5/593 (1%, includes both arms of trial)

(Continues)

TABLE 1 (Continued)

Parameter	Study			
	Rosen et al. [9] (RAPiT)	**Labhardt et al. [10] (CASCADE)**	**Rosen et al. [11] (SLATE I)**	**Maskew et al. [12] (SLATE II)**
ART initiation and retention outcomes – whole group exposed to TB screening algorithm				
No. actually initiating same-day ART	135/187 (72%)	134/137 (98%)[a]	Overall – 328/538 (61%)[b] South Africa, 161/298 (54%); Kenya, 167/240 (70%)	257/296 (87%)
No. initiating ART within 28 days	179/187 (96%)	136/137 (99%)[a]	Overall – 458/538 (85%) South Africa, 232/298 (78%); Kenya, 226/240 (94%)	277/296 (94%)
Initiated on ART and retained in care	151/187 (81%) at 10 months	94/137 (69%) at 3 months	Overall: 298/538 (55%) South Africa, 161/298 (54%); Kenya, 137/240 (57%)	220/296 (74%) at 8 months
Viral load measured and undetectable at 5–12 months	119/187 (64%)	69/137 (50%)	Overall – 181/538 (34%) South Africa, 93/298 (31%); Kenya, 88/240 (37%)	130/296 (44%)
Immune reconstitution inflammatory syndrome (IRIS)	Not reported	0/137 (0%)	Not reported	0/296 (0%)[c]
Mortality	No participants known to have died by 10 months [24 (13%) lost to follow-up]	2/137(1.5%) by 12 months [12 (8.8%) lost to follow-up)	9/538 (2%) by 8 months [135 (25%) lost to follow-up]	2/296 (1%) by 8 months [50 (17%) lost to follow-up]
ART initiation and retention outcomes – participants with one or more TB symptom and exposed to TB screening algorithm				
No. of those with TB symptoms who initiated same-day ART	5/29 (17%)	2/2 (100%)	Overall – 39/202 (19%) South Africa, 9/109 (8%); Kenya, 30/93 (32%)	104/140 (74%)

Abbreviations: ART, antiretroviral therapy; LAM, lipoarabinomannan; mITT, modified intention to treat; TB, tuberculosis.

[a]Based on readiness statements of participants at enrolment: 134 and 136 declared to start ART on the same day and within the coming days, respectively.

[b]Includes 48 people who were 'ineligible' for same-day ART according to SLATE I algorithm (39 due to TB symptoms, nine due to other reasons), but were nonetheless started on same-day ART by usual care services.

[c]No ART- or TB-related adverse events reported.

participants at primary care clinics in South Africa and Kenya were eligible to start same-day ART only if they had no TB symptoms (i.e. no cough, fever, night sweats or weight loss) – if a participant reported TB symptoms, they were referred to the routine services in that clinic to start ART under non-study procedures [11]. In SLATE II, people in primary care in South Africa (the same clinics as SLATE I), could start ART if they had TB symptoms

as long as urine lipoarabinomannan (LAM) lateral flow test was negative and the symptoms were not 'severe' [12]. All participants in SLATE II (regardless of TB symptoms) were asked to provide sputum for Xpert and traced with results the following day, but ART was not deferred while waiting for Xpert results.

In RapIT, 29/187 (16%) people assessed for same-day ART eligibility reported TB symptoms and 4/187 (2%) were diagnosed with TB at baseline. Overall, 135/187 (72%) actually started same-day ART, including 5/29 (17%) of those with one or more TB symptoms (possibly because they received a same-day negative Xpert result, although this is not explicitly stated). Overall, 119/187 (64%) people were retained in care, had a viral load taken and had an undetectable viral load measured within 12 months after study enrolment.

During home-based HIV testing that served as a platform for recruitment into CASCADE, 2/137 (1.5%) participants who newly tested HIV-positive, were not already on ART and were assigned to the same-day ART arm reported TB symptoms, but no-one was diagnosed with TB, either at enrolment or during follow-up. At one year, in the same-day arm, 69/137 (50%) were retained in care with a documented undetectable viral load, 4/137 (3%) had an unsuppressed viral load, 15/137 (11%) were in care without viral load measurement and the remaining 49/137 (36%) never linked to clinic ART care.

In SLATE I, 202/538 (47%) people being assessed for same-day ART reported TB symptoms and 21/538 (4%) were diagnosed with TB at baseline. Overall, 258/538 (48%) were ineligible for same-day ART, mainly due to the presence of TB symptoms. A total of 181/538 (34%) were retained in care with supressed viral load at 8 months: this relatively low proportion was often due to viral load testing not being done rather than proven virological failure. Of note, in SLATE I, 39 (7% total, 19% of those with TB symptoms) people were 'ineligible' for same-day ART implemented by SLATE study staff due to the presence of TB symptoms, but were nonetheless started on ART on the same day by the government usual care staff.

In SLATE II, 140/296 (47%) participants had one or more WHO TB symptom. However, as participants with TB symptoms remained eligible for same-day ART in SLATE II, only 41/296 (14%) participants were ineligible for same-day ART. Seven people (2%) were diagnosed with TB as a result of investigations initiated at baseline; two of these had been assessed as eligible and started on same-day ART, a third person was assessed as ineligible by SLATE II algorithm but was started on same-day ART by the usual care services. Six out of seven people with TB at baseline had TB symptoms. No harms were reported. Overall, 130/296 (44%) participants were retained in care and achieved viral suppression at 8 months. The low rate of viral suppression was mainly driven by viral load records missing at the predefined endpoint window of 5–18 months.

We identified a further 27 observational studies (30 articles) that reported some details of cohorts of participants starting same-day or rapid ART [13-42]. Only six studies made any mention of TB screening or of a group of participants who were clinically ineligible to start same-day ART. In a same-day ART programme in Thailand (three studies), authors report that TB screening was undertaken by physicians, but without providing details of how many people were either diagnosed with TB or had to defer ART initiation to await results of TB tests [21-23]. One study reported results from an HIV testing and same-day ART programme for key populations in Nigeria. Out of 709 who started same-day ART, nine (1.2%) had TB signs (these were not defined in the paper). The TB screening procedure was not detailed and 211 people were reported to have positive HIV tests in a community testing campaign but did not start ART for unstated reasons [15]. Two studies mentioned TB screening in the context of same-day ART among pregnant women, both in South Africa. In one study of 628 women, 'seven women experienced delay to ART initiation associated with diagnosis of TB in pregnancy', but it is not reported how these women were diagnosed with TB, or if any other women had a delay in ART as a result of symptoms that were ultimately not due to TB [32]. In the other study 16/134 pregnant women who were assessed were ineligible for same-day ART start and in 5/16 this was due to a requirement for a medical referral for 'suspected TB'. All five women subsequently had negative TB cultures [27]. The remaining 21 observational studies of same-day ART (including 14 in low- and middle-income countries) make no mention of TB screening procedures prior to same-day ART (Appendix S1).

We reviewed 16 other trials of either TB screening among people starting ART or rapid ART initiation at second full-text review. These were ineligible mostly due to exclusion of people with TB symptoms before enrolment or because they were evaluating rapid (but not same-day) ART; details are included in Appendix S2.

Study quality assessment

None of the included studies were designed to address directly the question of which TB symptoms preclude safe same-day ART initiation. If South Africa clinics in SLATE I and SLATE II were considered a before/after comparison and compared this with a target trial using ROBINS-i, there would be a high risk of bias due to lack of controlling for confounding, confounding due to deviations from intended interventions and missing outcome data.

DISCUSSION

We systematically reviewed the literature for studies that reported TB symptom screening interventions in order to determine eligibility for same-day ART initiation. There were no trials that directly compared two different methods of TB screening to determine eligibility for same-day ART. We identified four studies, all of which were randomized trials of same-day ART initiation (for those eligible) versus standard ART initiation, and included data from the group randomized to potential same-day ART for this review. Our main finding was that in two studies, a policy of deferring ART for people with TB symptoms led to large proportion of people unable to start same-day ART. In two studies, a policy of allowing some people with TB symptoms to start same-day ART meant more people started same-day ART, with no clear evidence of harm. Retention in care and viral load suppression at 8–12 months were relatively low in all four studies (varied between 34% and 64%) and it was not possible to determine whether TB screening approaches made a difference to this.

Tuberculosis symptoms are common among PLHIV not taking ART with pooled prevalence of 71% in a systematic review of 11 studies [7]. In the studies included for this review, the prevalence of TB symptoms was lower (ranging between 1.5% in the home-based CASCADE study to 47% in the clinic-based SLATE II). The large difference in prevalence of TB symptoms may be partly explained by the CASCADE trial enrolling individuals who tested positive during home-based HIV testing, whereas RapIT and SLATE I and II enrolled patients at clinics. Two included studies (RapIT and SLATE I) described same-day ART initiation only for those without TB symptoms (as suggested in the 2017 ART Guidelines [3]). Combined with the high prevalence of TB symptoms, this resulted in a substantial proportion of participants being ineligible for same-day ART. In SLATE I, people who had TB symptoms were less likely to initiate ART within 28 days than those without TB symptoms (not reported in RapIT).

By contrast, the two other included studies (CASCADE and SLATE II) took a more permissive approach, allowing same-day ART initiation in some people with TB symptoms while investigation results were pending, leading to greater proportion of people starting same-day ART than in RapIT and SLATE I (which had a more restrictive approach to same-day ART eligibility). An indirect before/after comparison shows that using the more permissive SLATE II algorithm allowed more people to initiate same-day ART (87% vs. 61%) and to initiate ART within 28 days (94% vs. 85%), and that more people were virologically suppressed at 8–14 months (44% vs. 37%), compared with the more restrictive SLATE I algorithm. This comparison has a high risk of bias. Even in groups with a high prevalence of TB symptoms, diagnosed TB disease at baseline was uncommon, ranging between 0% to 4%. No adverse events related to TB and no episodes of TB-IRIS were reported in either CASCADE or SLATE II.

In 21/27 of the other observational studies we reviewed, there was no mention at all of TB screening prior to same-day ART initiation. It was unclear whether this was because TB screening was done but the results were not reported, or because TB screening was not performed.

There are some limitations to our review. We only reviewed studies published in English. Our outcome of interest (TB screening to determine same-day ART eligibility) was not the main focus of any of the studies, and some outcomes were difficult to extract. We corresponded with authors of all included trials for additional details, but did not speak to authors of all observational studies or abstracts included to determine if there was more information available. A further limitation is the small number of studies and that they have only come from three countries, which limits generalizability.

In recent years, there has been a shift to earlier ART for most PLHIV. 'Treat all' (i.e. ART initiation at any CD4 count) was recommended by WHO in 2015, and, in 2017, same-day ART start was recommended [3,43]. Same-day ART has been shown to reduce pre-treatment loss to follow-up for HIV [44] and is preferred by many PLHIV, but most trials have excluded people with TB or TB symptoms. For people with diagnosed pulmonary TB, ART is recommended to be started relatively soon after TB treatment initiation following results from several trials showing that earlier ART (within 2 weeks) reduces deaths compared with later ART [43,45]. In some programmatic settings, ART and TB treatment are recommended to be started concurrently.

While there are still some questions about how early ART should be started in people with diagnosed TB, the group of people with TB symptoms but without firmly diagnosed TB is a much larger population. Most people (unless they have their HIV diagnosed following a TB diagnosis) do not have TB either clearly diagnosed or firmly refuted at the start of their assessment for ART. So while people without TB symptoms can start same-day ART, and people with confirmed TB in some settings can start same-day ART and TB treatment, it is possible that people with TB symptoms but not confirmed TB might face delays and perhaps multiple clinic visits before starting ART. In many settings, ART is delivered through a 'public health approach' [46], with task shifting to lower cadres of healthcare worker. Therefore guidelines should be as clear as possible to allow healthcare workers to carry out their roles with confidence.

Anecdotally, some ART providers are already moving towards starting some people with TB symptoms on same-day ART; we note that in SLATE I, 39 people who were ineligible for same-day ART according to the SLATE algorithm were nonetheless started on same-day ART by the usual care providers, perhaps after a more extensive clinical assessment. WHO guidelines from both 2017 and 2021 give 'clinical consideration' advice about same-day ART in people with TB symptoms. This is in place of a formal recommendation, as there was not enough evidence to make a recommendation. The 2021 guidelines suggest that for PLHIV with TB symptoms ART should be started 'while rapidly investigating for TB, with close follow up' and make note of the research gap in this area.

Finally, it is increasingly clear from TB screening surveys that absence of symptoms does not rule out TB, particularly in PLHIV [7,47,48]. It is likely that PLHIV without TB symptoms might benefit from TB tests if resources permit, and if this does not delay ART initiation. In addition, clinically incident TB after starting ART is relatively common, even with extensive screening prior to ART initiation. For example, in the STATIS trial [49], 67/522 people were diagnosed with TB in the year after starting ART even though everyone had negative TB tests (urine LAM, chest X-ray and sputum Xpert) prior to ART start. Rather than being an adverse event, unmasking TB around the start of TB treatment may be the opportunity for TB to be detected that was not possible before ART initiation. Deciding that someone does not have TB is a complex process: a single negative sputum NAAT does not rule out TB, and many people with TB symptoms are unable to produce sputum for testing. For these reasons, it is probably unhelpful to conceive of TB screening as an activity that can be carried out within a single day prior to ART initiation, and which can clearly divide people into one group who do not need TB tests and can start ART, and a second group who require ART deferral pending TB test results, in whom a negative test definitively excludes TB. Instead, research could be conducted to assess the benefits and harms of diagnosing or ruling out TB as a process conducted over a period of days or short weeks as test results become available and the clinical situation evolves, while not delaying ART start. This could be part of a differentiated care programme, so that, for example, people with TB symptoms or at high risk of IRIS would have closer follow-up around the start of ART initiation than those who are asymptomatic and starting ART with relatively preserved CD4 cell count. Some people would remain clinically inappropriate for same-day ART: for example, those who are not psychologically ready for ART, or who have signs and symptoms of central nervous system infection.

In summary, we identified only four studies that described TB screening to determine eligibility for starting same-day ART and reported the outcomes of everyone exposed to the TB screening algorithm. None of these studies had evaluation of TB screening interventions as their primary aim. Two studies showed that by deferring ART in all people with TB symptoms, relatively large proportions of people could not access same-day ART. Two studies showed that adopting a more permissive approach to same-day ART allowed more people to access ART. A comparison of two sequential studies showed that adopting a more permissive approach to same-day ART may have caused more people to achieve retention in care and viral suppression at 12 months. This is an important issue that affects large numbers of people as they start ART. The safety of same-day ART in some people with TB symptoms should be investigated in a randomized trial or in a high-quality prospective study using programmatic data, in order to develop and inform guidelines that could be adapted for use by all cadres of healthcare workers so that as many people as possible can start ART in an appropriately timely manner.

ACKNOWLEDGEMENTS

This work was funded by WHO Global HIV, Hepatitis and STI programme. RMB and PM are funded by Wellcome (203905/Z/16/Z and 206575/Z/17/Z, respectively). RJW is supported in part by Wellcome (104803, 203135). RJW was supported by the Francis Crick Institute which receives core funding from Cancer Research UK (FC0010218), the UK Medical Research Council (FC0010218) and Wellcome (FC0010218).

We acknowledge assistance of Jane Falconer (specialist librarian at LSHTM) for assistance with designing and running the search, and Nandi Siegfried (methodologist, Cochrane Collaboration) for comments on an earlier version of the report of this work.

CONFLICT OF INTEREST

All authors declare no financial or commercial conflicts of interest. NL is the principal investigator for the CASCADE trial which is included in this review. All other authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

RMB, HMR, VS, MH, RJW and PM conceived and designed the review. RMB designed the search strategy. RMB, HMR, PM and RJW reviewed texts for inclusion. RMB and HR extracted data. RMB, HMR and PM wrote the first draft. All authors revised the text for intellectual content.

RIGHTS RETENTION

This research was funded in whole or in part by Wellcome (203905/Z/16/Z, 206575/Z/17/Z, 104803, 203135). For

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DATA AVAILABILITY STATEMENT

All data associated with this article are contained in the manuscript and supplementary material.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of the article at the publisher's website.

How to cite this article: Burke RM, Rickman HM, Singh V, et al. Same-day antiretroviral therapy initiation for people living with HIV who have tuberculosis symptoms: a systematic review. *HIV Med*. 2022;23:4–15. https://doi.org/10.1111/hiv.13169