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An overview of systematic reviews on strategies to improve treatment initiation, adherence to antiretroviral therapy and retention in care for people living with HIV

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An overview of systematic reviews on strategies to improve treatment initiation, adherence to antiretroviral therapy and retention in care for people living with HIV

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ABSTRACT

Objectives

Interventions that support engagement along the care cascade for people living with HIV should target populations who are most in need and be applicable outside of research environments. In this overview of systematic reviews, we sought to identify effective pragmatic interventions that increase initiation of antiretroviral therapy (ART), adherence and retention in care for people living with HIV at high risk for poor engagement in care.

Methods

We searched PubMed, EMBASE, CINAHL, PsycINFO, Web of Science and the Cochrane Library in November 2018. We included studies that targeted men who have sex with men [MSM], African, Caribbean and Black [ACB] people, sex workers [SW], people who inject drugs [PWID], indigenous peoples and other socially marginalised groups.

Results

Of 2420 records, 98 systematic reviews were eligible. Some studies covered more than one aspect of the ART care cascade: initiation (n=18), adherence (n=82) and retention (n=39). Overall, 65/98 (66.3%) were judged to be at low risk of bias. The included systematic reviews focused on: ACB (66/98; 67.3%), MSM (32/98; 32.7%), PWID (6/98; 6.1%), sex workers (SW) and prisoners (both 4/98; 4.1%). The types of interventions reported were: mixed (37/98; 37.8%), digital (22/98; 22.4%), behavioral or educational (9/98; 9.2%), peer or community-based (8/98; 8.2%), health system (7/98; 7.1%), medication modification (6/98; 6.1%), economic (4/98; 4.1%), pharmacy based (3/98; 3.1%),or task-shifting (2/98; 2.0%). Most of the reviews concluded that the interventions worked (69/98; 70.4%), 17.3% (17/98) were neutral and 12.2% (12/98) were indeterminate. Digital, mixed and peer/community-based interventions were reported to be effective.

Conclusions

Interventions along the care cascade are mostly focused on adherence and do not sufficiently address all vulnerable populations. Understanding which interventions are effective, pragmatic and relevant to subpopulations require high quality pragmatic trials, with the right interventions for the right sub-populations and in-depth analysis of trial-level data.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To the best of our knowledge, this is the first overview to address the whole cascade of care for people living with HIV
- We categorized studies to facilitate data synthesis, however we acknowledge that certain interventions may fit into multiple categories
- Among mixed interventions, it was challenging to determine the role of the individual intervention types on the overall effect
- Our categorization of systematic reviews by intervention type and the intervention's success will permit decision makers to easily identify the interventions that are likely to work for their specific context

BACKGROUND

Despite advances in diagnosis and management of HIV infection, many people living with HIV still do not have optimal outcomes. In 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDS) set the 90-90-90 target for 2020.[1] If this target is met, 90% of people living with HIV will know their HIV status; 90% of all people diagnosed with HIV will be receiving antiretroviral therapy (ART) and 90% of all people on ART will be virally suppressed.[1] These targets are contingent on engagement in the cascade of care that includes access to testing, timely diagnosis, access to and initiation of treatment, adherence to treatment and retention in care. Despite national efforts, very few countries have actually met these targets.[2] The UK has met these targets[3] and Botswana and Australia are on track.[4] Canada is also on track to meet these targets, with 87% of people with HIV diagnosed, 82% on treatment and 93% virally suppressed.[5] For countries to meet these targets, there must be policies in place to support programs that deliver interventions across the entire cascade of care. As such, there must be awareness, reductions in stigma and incentives that promote testing alongside strategies to enhance treatment initiation, adherence and retention in care. [6] Consistent access to ART and high-quality data should be collected so that advances towards the targets can be measured appropriately.[6]

If all these conditions are met and countries meet these targets, there are still concerns that the targets may be met at a national level but not in certain sub-populations. [7,8] The literature suggests that vulnerable populations such as men who have sex with men (MSM), sex workers (SW), people who inject drug (IDU), people with precarious migration status and ethno-racial minorities have a higher disease burden, worse engagement in care and are less likely to achieve viral suppression.[9-14] MSM and SWs all over the worlds are 19 and 13.5 times more likely to be living with HIV.[7,8] In Canada, inequities in social and structural determinants such as injection drug use, ethno-racial background, age, housing, sex work and gender affect engagement in care.[11-15]

The literature is rife with interventions aimed at improving different aspects of the care cascade. However, the challenges countries face in achieving the UNAIDS targets suggests that the interventions may not be effective, may not be properly translated into practice, or may not be tailored to the relevant populations. Therefore, due consideration of the settings in which interventions are tested, their target populations, complexity and applicability in the real world are important considerations for scale up.[16,17] These limitations in the quality and quantity of evidence were identified in the International Association of Physicians in AIDS Care (IAPAC) guideline document.[18]

As countries strive to meet the 90-90-90 targets, it is becoming apparent that due to the disparities in outcomes across jurisdictions and populations, better targeted approaches are required to improve engagement in care.[19] Ontario is the most populous province of Canada and home to 42% of Canada's 71000 people living with HIV. Due to individual, social and structural factors, it is estimated that approximately 20% of these people living with HIV in Canada have discontinuous care.[11] In Ontario, 80-87% of people living with HIV are in care, 70-82% are on ART and 67-81% are virally suppressed.[20] This overview of systematic reviews will inform policy, practice and research in Ontario and other high-income settings especially with regards to engagement in HIV care for vulnerable populations. We sought to summarise the available evidence on strategies that improve engagement in the HIV care cascade for priority populations in high income countries and as well as to identify knowledge gaps.

METHODS

We conducted an overview of systematic reviews using standard Cochrane methods.[21] The protocol for this overview has been published elsewhere.[22] Key features of our methods are outlined below.

Patient and public involvement:

Our research question was formulated and refined based on input from the Ontario HIV Treatment Network (OHTN), a non-profit network, as part of their strategy to close gaps in the cascade of care for key populations. The investigators include patients, clinicians, researchers and representatives of AIDS Service Organizations/Community-Based Organizations (ASO/CBOs). Decision makers and representatives from the Ministry of Health and Long-Term Care (MOHLTC) of Ontario were also consulted.

Criteria for considering reviews for inclusion

We included any systematic reviews with at least one study with a randomized comparison of an intervention designed to improve initiation of ART, adherence to ART and/or retention in care among people living with HIV. We excluded abstracts, non-systematic reviews and other overviews. All comparators (e.g. attention control, usual care, another intervention etc.) were eligible for inclusion.

Search methods for identification of reviews

We conducted an exhaustive and comprehensive search of the following databases: PubMed, EMBASE (Exerpta Medica Database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), PsycINFO, Web of Science and the Cochrane Library; from1995 (when combination ART was introduced) to 13 November 2018. The search strategy was reviewed by a Librarian at Health Sciences Centre Library at McMaster University. The full search strategy is reported as a supplementary file.

We also searched the websites of the World Health Organization (WHO), United Nations Programme on HIV/AIDS (UNAIDS), National Institute for Health and Care Excellence (NICE) and the systematic review database housed at the the Ontario HIV Treatment Network (OHTN): Synthesized HIV/AIDS Research Evidence (SHARE; http://www.hivevidence.ca/frmSearch.aspx).

Finally, we looked for additional systematic reviews in the bibliographies of the included reviews.

Screening

The results of our search were collated in EndNote reference manager.[23] Duplicates were removed and all the references were uploaded unto DistillerSR (Evidence Partners, Ottawa, Canada). We screened the retrieved citations in duplicate with reviewer pairs (BZ, AW, AH) first by examining the titles and abstracts and secondly by examining the full texts. Systematic reviews that met our inclusion criteria were processed and data were extracted.

Data items

From the systematic reviews, we extracted standard bibliometric data (author, year), number of included studies and their designs, target populations, types of interventions, outcomes of interest, key findings and knowledge gaps. Data were extracted in duplicate by reviewers working in pairs (BZ, AW, AH).

Assessment of methodological quality of included reviews

We appraised the methodological quality of the included reviews using the risk of bias in systematic reviews (ROBIS) tool.[24] This tool allows reviewers to assess the relevance of the question, identify concerns with the review process and make a judgement on risk of bias (high, low, unclear). Risk of bias was appraised in duplicate by pairs of reviewers (BZ, AW, AH).

Discrepancies and disagreements in screening, data extraction and risk of bias were resolved by consensus or by adjudication by a third reviewer (LM).

Data synthesis

The extracted data were described narratively. Systematic reviews were organised according to the portion of the care cascade they addressed (i.e. initiation, adherence, retention) and the intervention types: behavioral or educational, digital, mixed, economic, health system, medication modification, peer or community-based, pharmacy based or task-shifting. These categories were developed post-hoc to facilitate data synthesis. The types of interventions included in each category are outlined in Table 1.

Table 1: Categorization of intervention types in the systematic reviews

Intervention category	Types
Behavioral & Educational	Medication-assisted therapy, mindfulness-based stress reduction, motivational interviewing, psychotherapy, relaxation
Digital	Digital technology-based interventions such as alarms, electronic pillboxes, and pagers, mobile device text messages and voice messages, computer-based or internet-based interventions, online support communities and electronic medication packaging
Mixed	Combinations of any of the listed categories
Economic	Food assistance, cash incentives, performance-based financing, household economic strengthening
Health system	Point of care services, decentralised services, less frequent visits
Medication modification	Single tablet regimens, fixed dose combinations, rapid medication initiation, observed therapy
Peer or community-based	Home-base care, community-based services including the use of community health workers, lay health workers, treatment buddies, field officers, peer educators, volunteers and counsellors.
Pharmacy-based	Changes to standard pharmacy service delivery, pharmacist delivered interventions
Task-shifting	Service delivery by non-doctor staff, nurse-led interventions

Conclusion statements were categorized according to a previously used framework: positive (evidence of effectiveness); neutral (no evidence of effectiveness or no opinion); negative (authors advise against the use of intervention); indeterminate (insufficient evidence or more research is required).[25] Knowledge gaps were operationalised according to guidance on how to report research recommendations by identifying the state of the evidence, participants, interventions, comparisons and outcomes for which further research is needed.[26] We also discuss our findings within the scope of the Health Systems Arrangement Framework. [27] In this framework, interventions may be organized to inform different parts of the decision-making process, and interventions can be related to governance, financial or delivery arrangements. [27] Interventions effects are summarised according to the vulnerable population they were tested with, intervention target (initiation, adherence, retention) and risk of bias. Interventions reported in systematic reviews at low risk of bias with positive recommendations are highlighted.

RESULTS

Literature search

Our search identified 2,420 records from electronic databases and 76 from other sources. After removal of duplicates, 1505 titles and abstracts were screened, of which 1006 were considered ineligible and excluded. We further screened 499 full text articles and included 98. Agreement on the screening of full text articles was high (Kappa=0.79). The screening process is outlined in a PRISMA flow diagram (Figure 1).[28] A full list of excluded studies is provided as a supplementary file.

Figure 1: Study flow diagram

Description of included reviews

The 98 included systematic reviews were published between 2006 and 2018[29-126] and reported on interventions to improve initiation of care (n=18),[30,39,52,56,59,62,63,68,73,76,79,82,90,98,107,111,121,124] adherence to ART (n=82)[29-34,36,37,39-51,53,55,57,58,60,63-66,69-75,77-106,108-110,112-114,116-120,122,123,125,126] and retention in care (n=39).[30,35,38,39,50,54,56-58,61-64,66-68,73-76,79,82,84,86,87,89-91,93,94,98,99,103,111,113-115,124,126] Thirty-one (31) reviews reported two or more aspects of the cascade.[30,39,50,56-58,62-64,68,73-76,79,82,84,86,87,89,90,93,94,98,99,103,111,113,114,124,126] They included a median (quartile 1; quartile 3 [Q1; Q3]) of 19 (11;28) studies and 8(4;13) randomized trials.

With regards to vulnerable populations, 32.7% (32/98) included studies involving MSM,[29,31,38-40,43,45,46,49,50,57,63,68,71,78,79,83,85,87,90,94,96-98,102-104,106,108,111,112,117] 67.3% (66/96) involving African, Caribbean or Black People,[29-32,34,35,38,41,43,45,46,48,50-52,54,56-59,61-64,68,69,71-80,82-85,87,88,90,91,93,99-102,104,106-108,110-118,121,123,124,126] 25.5% (25/98) focused on PWID,[37,39,41,42,46,48-50,58,64,66,68,71,72,83,86,89,90,94,97,98,103,106,114,119] 6.1% (6/98) involving SW,[39,40,46,50,94,98] 4.1% (4/98) included data on immigrants, [40,80,106,124] and 4.1% (4/98) included data on incarcerated persons.[38,58,89,103] These characteristics are summarised in table 2. A full list of the 98 included studies is reported as a supplemental file.

Table 2: Summary characteristics of included systematic reviews: n=98

Variable	**Statistic**
Year: median (quartile 1; quartile 3)	2015 (2013;2017)
Number of included studies: median (quartile 1; quartile 3)	29 (11; 28)
Number of randomized trials: median (quartile 1; quartile 3)	8 (4;13)
Vulnerable populations included: n (%)	
African, Caribbean or Black	66 (67.3)
Men who have sex with men	32 (32.7)
People who inject drugs	25 (25.5)
Sex workers	6 (6.1)
Immigrants	4 (4.1)
Incarcerated persons	4 (4.1)
Intervention categories: n (%)	
Mixed	37 (37.8)
Digital	22 (22.4)
Behavioral or educational	9 (9.2)
Peer or community based	8 (8.2)
Health system	7 (7.1)
Medication modification	6 (6.1)
Economic	4 (4.1)
Pharmacy	3 (3.1)
Task shifting	2 (2.0)
Care cascade outcomes: n (%) *	
Adherence	82 (59.0)
Retention	39 (28.1)
Initiation	18 (12.9)

*not mutually exclusive

Methodological quality of included reviews

Most of the systematic reviews were judged to be a low risk of bias (65 [66.3%]). Twenty (20.4%) were judged to be at high risk of bias and 13 (13.3%) were judged to be at unclear risk of bias. The most frequent concern was related to data collection and study appraisal (28.6% at high risk of bias in this domain). The main concerns we identified were no risk of bias assessments conducted, missing study information and no evidence that data had been processed in duplicate. This was followed by the risk of bias in the identification and selection of studies (19.4% at high risk of bias in this domain). The main limitations we identified were not searching grey literature, searching less than 2 databases, exclusion of non-English studies, no evidence that data were processed in duplicate and not reporting the search strategy. For the domain of study eligibility criteria (15.3% at high risk of bias in this domain) the main concerns were: eligibility criteria not described in sufficient detail, ambiguous criteria and restrictions based on publication status and language. For the domain of synthesis and findings (15.3% at high risk of bias in this domain) the main concerns were: heterogeneity was not assessed, choice of synthesis approach not justified and primary study biases not addressed. See Figure 2 and additional file 2.

Figure 2: Risk of bias in included reviews

Effects of interventions

Most systematic reviews gave positive recommendations for the interventions they examined (69/70.4%). Seventeen (17.3%) were neutral and 12 (12.2%) were indeterminate. No systematic reviews recommended against any interventions. Positive findings from systematic reviews at low risk of bias are outlined below.

Initiation

Of the 18 systematic reviews that examined initiation of ART as an outcome, 9 (50%) reported that digital,[39,98] mixed,[30,52,73,82] health system [64,76,121] and peer or community-based interventions [63,111] improved initiation of ART.

Adherence

Of the 82 systematic reviews that examined adherence to ART as an outcome, 25 (30.5%) reported that behavioral/educational,[42,43] digital,[29,31,39,44,50,77,96,98,99,109,120] mixed,[30,34,41,51,55,60,70,72,73,80,82,89,101,103,106,110] health system,[48] medication modification,[47,57,100] peer/community-based,[71,94,126] pharmacy[84,109] and task-shifting interventions[75] improved adherence to ART.

Retention

Of the 39 systematic reviews that examined retention in care as an outcome, 21 (53.8%) systematic reviews reported that digital,[39,50,98] mixed,[30,64,67,73,82,89,103] economic,[113] health system,[64,76,93] medication modification,[57] peer/community-based[63,94,111,126] and task shifting[75] interventions improved adherence to HIV care.

Knowledge gaps

The most frequent knowledge gap identified in 22 (22.4%) systematic reviews was with regards to the population studied, where further investigation with vulnerable and marginalized groups such as children, youth, MSM, pregnant and breast-feeding women, individuals in low-income settings, individuals with concurrent mental health issues and older adults is required. The authors also raised concerns about the study designs (n=22/22.4%), and primarily called for more robust, innovative, rigorous and high-quality designs, including experimental designs, (pragmatic) randomized trials, longer follow-up times, mixed methods approaches, and studies with larger sample sizes. The nature of the intervention was also identified as a knowledge gap (22/22.4%). The authors found that interventions were not sufficiently tailored

to high-risk populations, low-income settings, were too costly or didn't cover the entire cascade of care. They further suggested that novel interventions be investigated, and older intervention be combined to assess synergistic effects. Only two (2.0%) systematic reviews raised concerns about the nature of the outcomes used. They called for universal definitions for adherence and the use of more humanistic, economic and patient-important outcomes.

DISCUSSION

We conducted an exhaustive and comprehensive search for systematic reviews focused on examining interventions that enhance ART initiation, ART adherence and retention among people living with HIV. We included 98 systematic reviews. Most of the systematic reviews we identified focused on adherence enhancing interventions and investigated a mixed range of intervention categories. For the most part, the authors of the included systematic reviews found that the interventions were effective (70.4%). Digital, mixed and peer/community interventions were the only three categories of interventions that were reported to be effective across the whole continuum of care. The main knowledge gaps identified in most systematic reviews was a lack of focus on the populations that would benefit the most (22.4%), poor quality of the studies (22.4%) and nature of the interventions. (22.4%).

We further examined to what extent health systems arrangements were met by this body of evidence. Most studies focused on the delivery of interventions (task-shifting, homebased care, pharmacy-based interventions etc.) but none addressed governance of HIV care and very few addressed financial components (food assistance, cash incentives, performance-based financing, household economic strengthening) that may support or hinder access to HIV care and treatment. [53,66,113,114]

Most of the studies were at low risk of bias (66.3%).[24] However, there were some concerns, notably with issues related to reporting of details in review conduct which indicated high or unclear risk of bias. We recognise that journal word count limitations may prevent authors from reporting all the relevant details, but appendices could be used to provide additional details.

To the best of our knowledge, there is no other overview of systematic reviews investigating the cascade of HIV care, but our findings confirm previous research indicating a paucity of research on vulnerable populations,[127] and challenges with scaling-up interventions.[128]

The disproportionate study of adherence might be due to it's perceived importance as a cornerstone of care, or the relative ease of designing adherence studies. Prior to recent recommendations to treat all diagnosed people, initiation of treatment was seldom a priority. [129]Likewise, retention in care is an outcome that requires substantially longer follow up to generate meaningful results.[11,130]

Even though only disparate definitions of adherence to ART were identified by the authors of some systematic reviews, we believe such diversity may exist with retention in care, as other studies have noted that there is no gold standard for what constitutes adequate retention. [131] Future work on the trials included in the systematic reviews will permit us the describe the breadth of definitions used for both adherence and retention.

Strengths and limitations

We acknowledge the following limitations. Despite our attempt to group the interventions into categories, we recognise that certain interventions may fit into more than one category. For example, tasking shifting and pharmacy-based interventions can be viewed as health system or community-based interventions. Secondly, for the group of studies that investigated mixed interventions, it is challenging to determine the role of the individual intervention types on the overall effect. This group could contain interventions from

any category and therefore it is not surprising that the systematic reviews that included mixed interventions often found a significant effect. Within each systematic review, the diversity of study designs, populations and studies from various income levels precluded in-depth investigation of how these issues may have affected intervention effectiveness at the systematic review level. No distinction was made between ACB populations in their respective countries versus ACB populations in high income countries where the vulnerability is different. Further ongoing work on the trials included in these systematic reviews will highlight the features of interventions in ACB populations. Finally, some primary studies are included in more than one systematic review. This highlights the need for a primary study-level analysis.

This work has many strengths. In addition to using a predefined protocol, we conducted a comprehensive search, assessed risk of bias, investigated the availability of data on vulnerable populations and categorized the systematic reviews by type of intervention and success of the intervention. This approach would permit decision makers and other end users to identify intervention type that are likely to work for specific populations at each point of the care cascade. However, a trial-level analyses is required to enrichen these findings.

CONCLUSIONS

We found limited research on vulnerable populations and uneven focus on the three aspects of the care cascade. In order to identify the most effective and pragmatic interventions for vulnerable populations in high income settings, a study-level analysis is required. The diversity of the interventions examined and the populations studied indicate the need for network meta-analyses in this field, some of which have already been published.[88] The lack of systematic reviews that generate evidence on governance is indicative of how removed many research endeavours are from policy-making. Monitoring and evaluation also need to be considered within systems to support up-to-date collection of data on detection, initiation, adherence and retention in care.

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AUTHORS' CONTRIBUTIONS

LM developed the first draft of the manuscript. AH, AW, LM, BZ extracted data and created tables. EA, DOL, BR, MS, DM, LPR, CL, SM, AB, WH, AH, AW, BZ and LT revised several versions of the manuscript and approved the final version. LM is the guarantor of the manuscript.

DECLARATIONS OF INTEREST

The authors declare none.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are a few differences between this report and the protocol. First, after additional consultation with stakeholders we included interventions targeting initiation of ART. Given the amount of data, we decided to report our findings on two levels, the systematic review level and the primary study level. Only the systematic review level is reported here, and therefore in-depth analyses of the settings (high versus low income) of the primary studies and the levels of pragmatism are reserved for a second paper.

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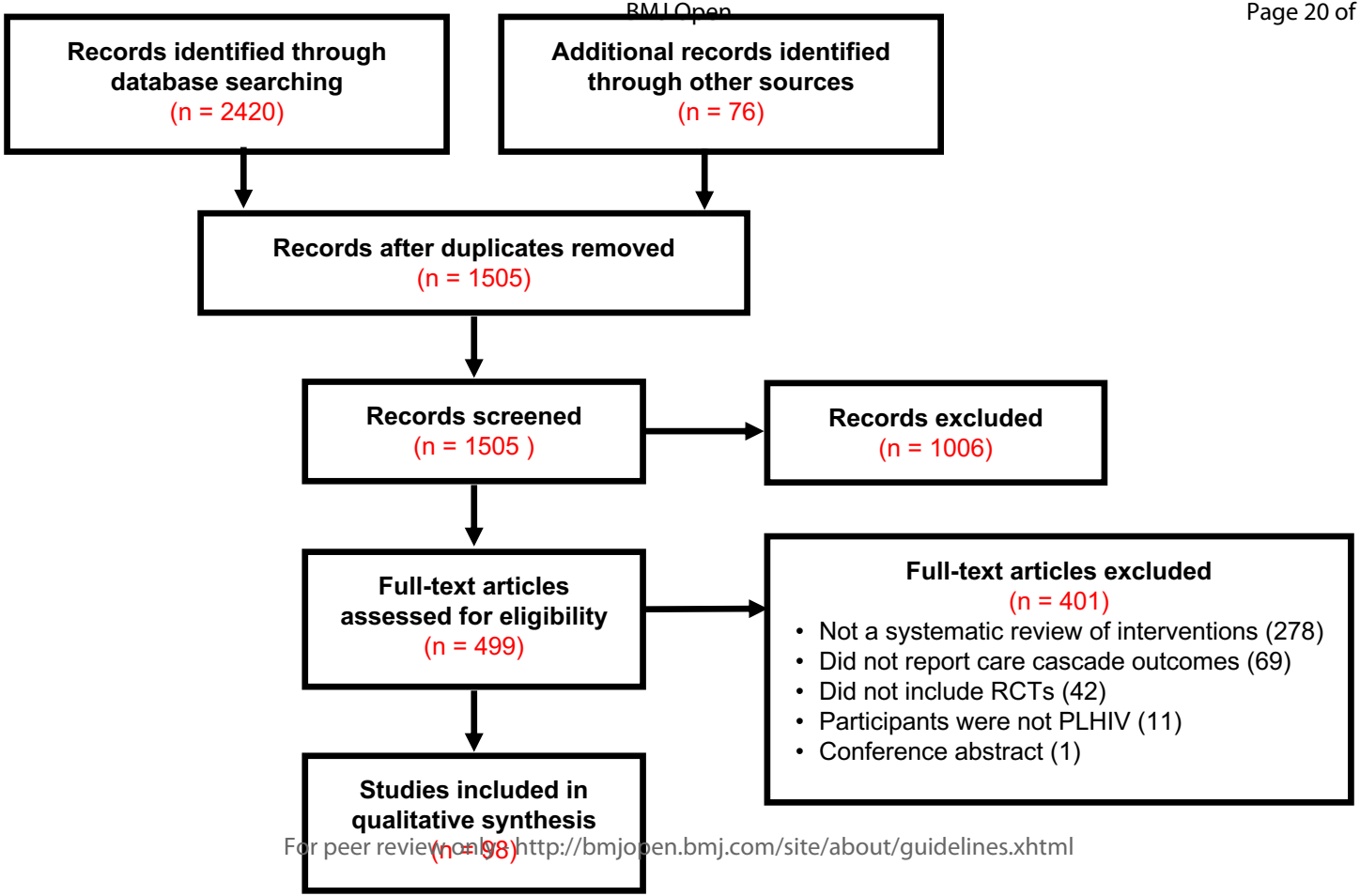

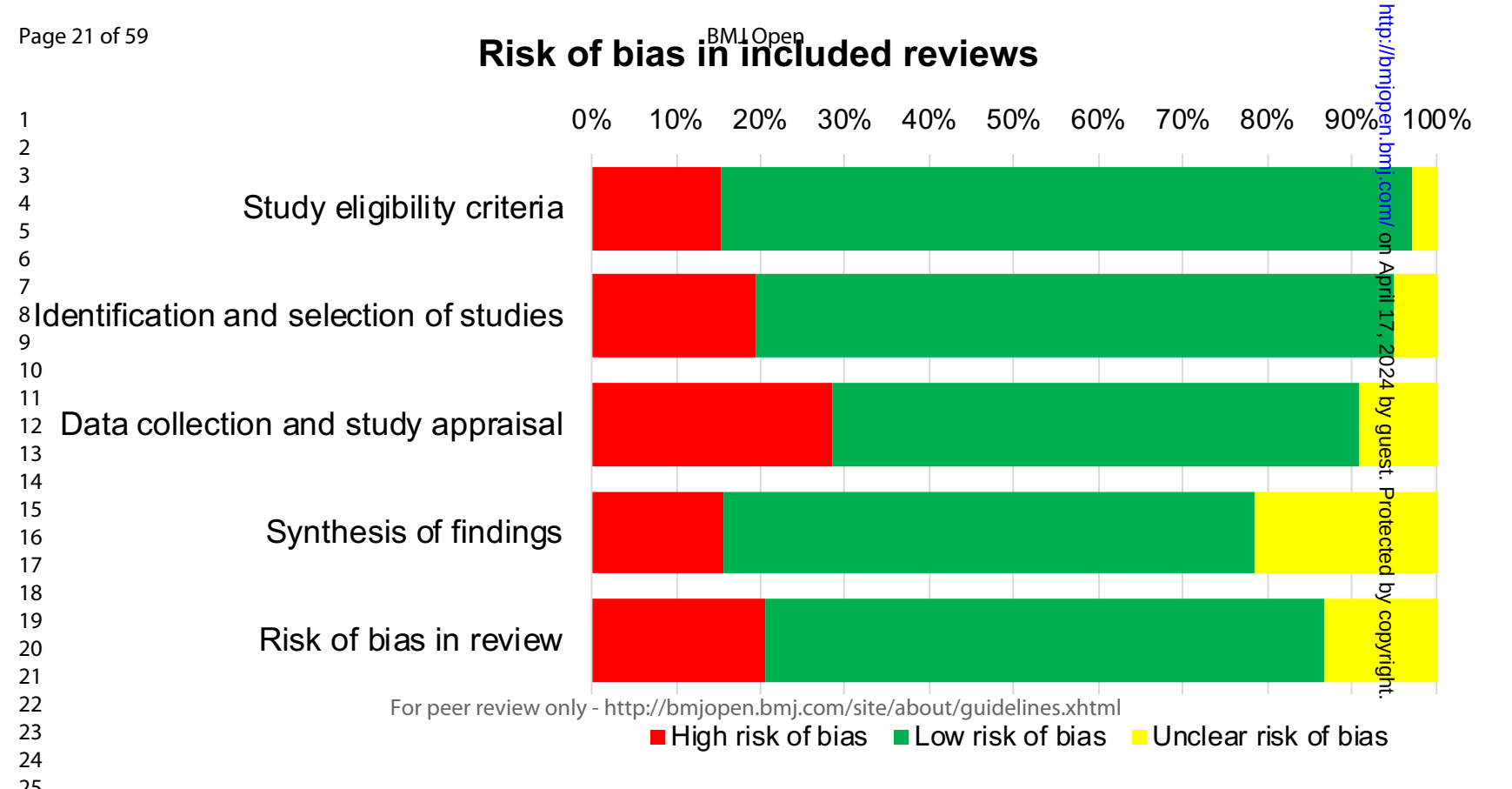

Supplement 1: Search strategy

Database: CINAHL via EBSCOhost Research Databases

Completed on: November 13, 2018

Search Strategy:

S1	(MH "Systematic Review")	68,246
S2	(MH "Meta Analysis")	35,345
S3	S1 OR S2	87,072
S4	(MH "Patient Compliance+") OR (MH "Treatment Refusal") OR (MH "Medication Compliance")	46,042
S5	(MH "Research Subject Retention")	692
S6	(MH "Research Dropouts") OR (MH "Patient Dropouts")	2,506
S7	(MH "After Care")	11,133
S8	adhere* OR nonadhere* OR complian* OR uncomplian* OR retention OR dropout OR lost to follow-up OR attrition OR treatment refusal OR persistence OR non-persistence OR initiat* OR start* OR uptake	339,844
S9	S4 OR S5 OR S6 OR S7 OR S8	349,538
S10	(MH "Human Immunodeficiency Virus+")	8,168
S11	(MH "HIV-Infected Patients+") OR (MH "HIV Infections+")	80,662
S12	HIV OR human immun* deficiency virus	96,874
S13	S10 OR S11 OR S12	104,864
S14	(MH "Antiretroviral Therapy, Highly Active")	5,519
S16	antiretroviral therapy OR antiretrovirals OR antiretroviral treatment OR anti-HIV agents OR anti-retroviral agents OR Highly Active Antiretroviral Therapy OR HAART	24,400
S17	S14 OR S15 OR S16	26,013
S18	S3 AND S9 AND S13 AND S17	**195**

(Limiter: Published Date: 19950101-20181231)

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Database: Cochrane Database of Systematic Reviews

Completed on: November 13, 2018

Search Strategy:

'adhere* OR nonadhere* OR complian* OR uncomplian* OR retention OR dropout OR lost to follow-up OR attrition OR treatment refusal OR persistence OR non-persistence OR initiat* OR start* OR uptake in All Text AND HIV OR human immun* adj2 deficiency virus in All Text AND antiretroviral therapy OR antiretrovirals OR antiretroviral treatment OR anti-HIV agents OR anti-retroviral agents OR Highly Active Antiretroviral Therapy OR ART OR HAART in All Text - with Cochrane Library publication date Between Jan 1995 and Dec 2018 (Word variations have been searched)' **(217)**

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Database: Embase <1974 to 2018 November 09> via Ovid

Completed on: November 12, 2018

Search Strategy:

---

1 systematic review.mp. or exp "systematic review"/ (241913)

2 meta analysis.mp. or exp "meta analysis"/ (232198)

3 (complian* or uncomplian*).mp. or exp "medication compliance"/ (306191)

4 retention.mp. (225178)

5 dropout.mp. or exp "patient dropout"/ (10447)

6 (los* adj2 to follow up).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (35898)

7 attrition.mp. (14277)

8 (adhere* or nonadhere*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (255209)

9 treatment refus*.mp. or exp "treatment refusal"/ (17490)

10 persistence.mp. (102883)

11 initiat*.mp. (789288)

12 start*.mp. (634133)

13 uptake.mp. (461506)

14 1 or 2 (366337)

15 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (2578956)

16 (HIV or human immune-deficiency virus or human immuno-deficiency virus).mp. (367212)

17 exp "human immunodeficiency virus"/ or exp "human immunodeficiency virus infection"/ or exp "human immunodeficiency virus infected patient"/ (452990)

18 16 or 17 (501218)

19 antiretroviral therapy.mp. or exp "antiretroviral therapy"/ (69407)

20 antiretrovirals.mp. (4928)

21 antiretroviral treatment.mp. (9740)

22 exp "antiretrovirus agent"/ (178047)

23 highly active antiretroviral therapy.mp. or exp "highly active antiretroviral therapy"/ (38980)

24 (ART or HAART).mp. (170581)

25 19 or 20 or 21 or 22 or 23 or 24 (340645)

26 14 and 15 and 18 and 25 (948)

27 limit 26 to yr="1995 -Current" **(947)**

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Database: PsycINFO <1987 to November Week 1 2018> via Ovid

Completed on: November 12, 2018

Search Strategy:

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1 systematic review.mp. (21950)

2 meta analysis.mp. or exp "meta analysis"/ (25527)

3 1 or 2 (41919)

4 exp "compliance"/ or exp "treatment compliance"/ (16310)

5 (complian* or uncomplian*).mp. (32297)

6 dropout.mp. or exp "treatment dropout"/ (7191)

7 retention.mp. (34515)

8 attrition.mp. or exp "experimental attrition"/ (6818)

9 (los* adj2 to follow up).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (1103)

10 adhere*.mp. (31235)

11 treatment refus*.mp. or exp "treatment refusal"/ (886)

12 persistence.mp. (16819)

13 initiate.mp. (9915)

14 start*.mp. (82553)

15 uptake.mp. (13475)

16 nonadherence.mp. (1750)

17 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (215604)

18 HIV.mp. or exp "HIV"/ (52967)

19 (human immunodeficiency virus or human immune-deficiency virus or human immuno-deficiency virus).mp. (6071)

20 18 or 19 (53288)

21 exp "drug therapy"/ (121212)

22 (antiretroviral or antiretroviral therapy or antiretroviral treatment or ART or HAART).mp. (40678)

23 21 or 22 (158296)

24 3 and 17 and 20 and 23 (105)

25 limit 24 to yr="1995 -Current" **(105)**

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Database: PubMed <1995/01/01 to 31-Dec-2018>

Completed on: November 13, 2018

Search Strategy:

((((((systematic review OR meta-analysis)) AND (adhere* OR nonadhere* OR complian* OR uncomplian* OR retention OR dropout OR lost to follow-up OR attrition OR treatment refusal OR persistence OR non-persistence OR initiat* OR start* OR uptake)) AND (HIV OR human immune-deficiency virus OR human immuno-deficiency virus)) AND (antiretroviral therapy OR antiretrovirals OR antiretroviral treatment OR Highly Active Antiretroviral Therapy OR ART OR HAART OR anti-HIV agents OR anti-retroviral agents)) AND systematic[sb]) AND systematic review[ti] Filters: Publication date from 1995/01/01 to 2018/12/31

(304)

MeSH headings [mh], captured via 'All Fields' search:

meta-analysis [publication type], meta-analysis as topic / review, systematic

patient dropouts / patient compliance (patient adherence/nonadherence) / treatment adherence and compliance (therapeutic adherence/compliance) / medication adherence (nonadherence, compliance/noncompliance) /lost to follow-up

HIV / anti-HIV agents / anti-retroviral agents / antiretroviral therapy, highly active (HAART)

systematic review	"review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "systematic review"[All Fields]
meta-analysis	"meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields]
retention	"retention (psychology)"[MeSH Terms] OR ("retention"[All Fields] AND "(psychology)"[All Fields]) OR "retention (psychology)"[All Fields] OR "retention"[All Fields]
lost to follow-up	"lost to follow-up"[MeSH Terms] OR ("lost"[All Fields] AND "follow-up"[All Fields]) OR "lost to follow-up"[All Fields] OR ("lost"[All Fields] AND "follow"[All Fields] AND "up"[All Fields]) OR "lost to follow up"[All Fields]
attrition	"tooth attrition"[MeSH Terms] OR ("tooth"[All Fields] AND "attrition"[All Fields]) OR "tooth attrition"[All Fields] OR "attrition"[All Fields]
treatment refusal	"treatment refusal"[MeSH Terms] OR ("treatment"[All Fields] AND "refusal"[All Fields]) OR "treatment refusal"[All Fields]
HIV	"hiv"[MeSH Terms] OR "hiv"[All Fields]
human	"humans"[MeSH Terms] OR "humans"[All Fields] OR "human"[All Fields]
immune-deficiency	"immunologic deficiency syndromes"[MeSH Terms] OR ("immunologic"[All Fields] AND "deficiency"[All Fields] AND "syndromes"[All Fields]) OR "immunologic deficiency syndromes"[All Fields] OR ("immune"[All Fields] AND "deficiency"[All Fields]) OR "immune deficiency"[All Fields]
virus	"viruses"[MeSH Terms] OR "viruses"[All Fields] OR "virus"[All Fields]
immuno-deficiency	"immunologic deficiency syndromes"[MeSH Terms] OR ("immunologic"[All Fields] AND "deficiency"[All Fields] AND "syndromes"[All Fields]) OR

	"immunologic deficiency syndromes"[All Fields] OR ("immuno"[All Fields] AND "deficiency"[All Fields]) OR "immuno deficiency"[All Fields]
therapy	"therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]
treatment	"therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]
Highly Active Antiretroviral Therapy	"antiretroviral therapy, highly active"[MeSH Terms] OR ("antiretroviral"[All Fields] AND "therapy"[All Fields] AND "highly"[All Fields] AND "active"[All Fields]) OR "highly active antiretroviral therapy"[All Fields] OR ("highly"[All Fields] AND "active"[All Fields] AND "antiretroviral"[All Fields] AND "therapy"[All Fields])
ART	"art"[MeSH Terms] OR "art"[All Fields]
HAART	"antiretroviral therapy, highly active"[MeSH Terms] OR ("antiretroviral"[All Fields] AND "therapy"[All Fields] AND "highly"[All Fields] AND "active"[All Fields]) OR "highly active antiretroviral therapy"[All Fields] OR "haart"[All Fields]
anti-HIV agents	"anti-hiv agents"[Pharmacological Action] OR "anti-hiv agents"[MeSH Terms] OR ("anti-hiv"[All Fields] AND "agents"[All Fields]) OR "anti-hiv agents"[All Fields] OR ("anti"[All Fields] AND "hiv"[All Fields] AND "agents"[All Fields]) OR "anti hiv agents"[All Fields]
anti-retroviral agents	"anti-retroviral agents"[Pharmacological Action] OR "anti-retroviral agents"[MeSH Terms] OR ("anti-retroviral"[All Fields] AND "agents"[All Fields]) OR "anti-retroviral agents"[All Fields] OR ("anti"[All Fields] AND "retroviral"[All Fields] AND "agents"[All Fields]) OR "anti retroviral agents"[All Fields]

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Database: Web of Science

Completed on: November 13, 2018

Search Strategy:

#1	TS=(systematic review OR meta-analysis)	271,168
#2	TS=(adhere* OR nonadhere* OR complian* OR uncomplian* OR retention OR dropout OR los* follow-up OR attrition OR treatment refusal OR persistence OR non-persistence OR initiat* OR start* OR uptake)	2,512,891
#3	TS=(HIV OR human immun* deficiency virus)	306,952
#4	TS=(antiretroviral therapy OR antiretrovirals OR antiretroviral treatment OR anti-HIV agents OR anti-retroviral agents OR ART OR Highly Active Antiretroviral Therapy OR HAART)	461,846
#5	#4 AND #3 AND #2 AND #1	**652**

(Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1995-2018)

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Supplement 2: Characteristics of included studies

Study ID	Total studies (RCTs)	Key populations included	Intervention type	Target	Conclusion	Knowledge gaps	RoB
Amankwaa 2018[1]	13(13)	MSM, ACB	Digital	Adherence	Positive	Intervention	Low
Ambia 2016[2]	34(10)	ACB	Diverse	Retention	Positive	Design	Low
Anglada-Martinez 2015[3]	20(3)	MSM, ACB	Digital	Adherence	Positive	Design	Low
Arrivillaga 2013[4]	16(5)	ACB	Diverse	Adherence	Neutral	Population, Design	Unclear
Barnighausen 2011[5]	26(15)	ACB	Diverse	Adherence	Positive	Intervention	Low
Bateganya 2015[6]	20(1)	ACB	Behavioral	Retention	Positive	Population, Intervention	Unclear
Bhatta 2017[7]	28(28)	None	Diverse	Adherence	Neutral	Design	High
Bain-Brickley 2011[8]	4(2)	None	Diverse	Adherence	Neutral	Population	Low
Binford 2012[9]	45(15)	PWID	Behavioral	Adherence	Positive	Population	High
Brennan 2014[10]	5(5)	MSM, ACB	Health system	Retention	Positive	Design	High
Cao 2017[11]	26(8)	MSM, PWID, CSW	Digital	Retention	Positive	Population, Intervention	Low
Catalani 2013[12]	62(4)	MSM, Immigrants, CSW	Digital	Adherence	Positive	Evidence	High
Chaiyachati 2014[13]	124(19)	ACB, PWID	Diverse	Adherence	Positive	Population, Design	Low
Chang 2014[14]	12(9)	PWID	Behavioral	Adherence	Positive	Intervention, Design	Low
Charania 2014[15]	9(10)	MSM, ACB	Behavioral	Adherence	Positive	Evidence	Low
Checchi 2014[16]	37(34)	None	Digital	Adherence	Positive	Intervention, Design	Low
Cho 2017[17]	10(10)	MSM, ACB	Digital	Adherence	Indeterminate	Evidence, Outcome	Low
Claborn 2015[18]	10(6)	MSM, ACB, PWID, CSW	Digital	Adherence	Indeterminate	Intervention, Design	Low
Clay 2018[19]	63(34)	None	Medication modification	Adherence	Positive	Evidence	Low
Crepaz 2015[20]	15(15)	PWID	Health system	Adherence	Positive	Intervention	Low
Crepaz 2015[21]	15(8)	MSM, ACB, PWID	Diverse	Adherence	Positive	Evidence	High

Daher 2017[22]	99(38)	MSM, ACB, PWID, CSW	Digital	Retention	Positive	Population	Low
de Bruin 2010[23]	20(18)	ACB	Diverse	Adherence	Positive	Comparison	Low
de Jongh 2016[24]	12(2)	ACB	Diverse	Initiation	Positive	Evidence	Low
de Pee 2014[25]	10(0)	None	Economic	Adherence	Positive	Population, Design	Unclear
Decroo 2013[26]	18(2)	ACB	Peer or community based	Retention	Positive	Evidence	Unclear
Demonceau 2013[27]	79(30)	None	Diverse	Adherence	Positive	Design	Low
Feyissa 2014[28]	3(1)	ACB	Health system	Retention	Neutral	Evidence	Low
Ford 2009[29]	12(12)	ACB, PWID	Medication modification	Retention	Neutral	Intervention	Low
Ford 2018[30]	22(4)	MSM, ACB	Medication modification	Retention	Positive	Population	Low
Fox 2016[31]	22(10)	ACB	Diverse	Initiation	Neutral	Evidence	Low
Ganguli 2016[32]	64(8)	None	Diverse	Adherence	Positive	Intervention	Low
Gaston 2014[33]	13(4)	ACB	Diverse	Retention	Indeterminate	Evidence	High
Geldsetzer 2016[34]	10(4)	ACB	Digital	Retention	Positive	Evidence, Population	High
Genberg 2016[35]	9(8)	MSM, ACB	Peer or community based	Retention	Positive	Evidence, Intervention	Low
Govindasamy 2014[36]	24(5)	ACB, PWID	Diverse	Retention	Positive	Design	Low
Hart 2010[37]	17(11)	None	Medication modification	Adherence	Neutral	Design	Low
Herrmann 2017[38]	23(3)	PWID	Economic	Retention	Neutral	Evidence	High
Higa 2012[39]	13(4)	MSM, ACB, PWID	Diverse	Retention	Positive	Intervention, Design	Unclear
Higa 2016[40]	10(9)	None	Diverse	Retention	Positive	Evidence	Low
Higgs 2014[41]	26(4)	ACB	Digital	Adherence	Positive	Evidence	Unclear
Hill 2012[42]	5(5)	None	Diverse	Adherence	Positive	Evidence, Outcome	Low
Kanters 2016[43]	22(22)	MSM, ACB, PWID	Peer or community based	Adherence	Positive	Evidence, Design	Low

Kanters 2017[44]	85(87)	ACB, PWID	Diverse	Adherence	Positive	Population, Intervention, Design	Low
Keane 2017[45]	13(3)	ACB	Diverse	Retention	Positive	Intervention	Low
Knight 2018[46]	8(5)	ACB	Diverse	Retention	Indeterminate	Evidence, Population	Unclear
Kredo 2013[47]	16(2)	ACB	Health system	Retention	Positive	Design	Low
Kredo 2014[48]	10(4)	ACB	Task shifting	Retention	Positive	Population, Intervention, Design	Low
Lima 2016[49]	9(9)	ACB	Digital	Adherence	Positive	Intervention, Design	Low
Ma 2018[50]	23(9)	MSM, ACB	Diverse	Adherence	Positive	Design	High
MacPherson 2015[51]	11(3)	MSM, ACB	Diverse	Retention	Indeterminate	Population, Design	Low
Manias 2010[52]	46(9)	ACB, Immigrants	Diverse	Adherence	Positive	Intervention, Design	Low
Mathes 2013[53]	21(21)	None	Behavioral	Adherence	Neutral	Outcome, Design	Low
Mavegam 2017[54]	6(1)	ACB	Diverse	Retention	Positive	Evidence, Population	Low
Mayer 2017[55]	33(24)	MSM, ACB, PWID	Digital	Adherence	Positive	Population	High
Mbeye 2017[56]	3(3)	ACB	Pharmacy	Retention	Indeterminate	Evidence, Population, Intervention	Low
Mbuagbaw 2012[57]	28(4)	PWID	Behavioral	Adherence	Indeterminate	Evidence, Population	Low
Mbuagbaw 2015[58]	49(49)	MSM, ACB	Diverse	Adherence	Neutral	Population, Intervention, Design	Low
Medley 2015[59]	92(11)	MSM, ACB	Diverse	Retention	Positive	Population, Intervention	High
Mills 2014[60]	14(14)	ACB	Digital	Adherence	Positive	Population, Intervention	High
Mizuno 2018[61]	20(5)	PWID	Diverse	Retention	Positive	Design	Low
Muessig 2015[62]	23(21)	MSM, ACB, PWID	Digital	Retention	Indeterminate	Evidence	High
Murray 2017[63]	23(2)	ACB	Diverse	Retention	Indeterminate	Population	Unclear
Musayon-Oblitas 2018[64]	9 (9)	None	Behavioral	Adherence	Positive	Evidence, Intervention	Low
Mutasa-Apollo 2017[65]	11(3)	ACB	Health system	Retention	Positive	Evidence	Low
Nachega 2016[66]	22(11)	MSM, PWID, CSW	Peer or community based	Retention	Positive	Population, Design	Low

Parienti 2009[67]	11(11)	None	Medication modification	Adherence	Positive	None	High
Park 2014[68]	29(5)	MSM	Digital	Adherence	Positive	Intervention	Low
Perazzo 2017[69]	6(4)	MSM, PWID	Diverse	Adherence	Positive	Evidence	Unclear
Purnomo 2018[70]	16(7)	MSM, PWID, CSW	Digital	Retention	Positive	Design	Low
Quintana 2018[71]	26(19)	ACB	Digital	Retention	Neutral	Population, Intervention	Low
Ramjan 2014[72]	21(6)	ACB	Medication modification	Adherence	Positive	Evidence	Low
Ridgeway 2018[73]	52(29)	ACB	Diverse	Adherence	Positive	Population	Low
Riley 2015[74]	11 (6)	MSM, ACB	Behavioral	Adherence	Positive	Evidence, Intervention, Comparison	High
Risher 2017[75]	152(14)	MSM, PWID	Diverse	Retention	Positive	Evidence, Population, Intervention, Design	Low
Robbins 2014[76]	10(12)	MSM, ACB	Diverse	Adherence	Indeterminate	Population, Intervention, Design	Unclear
Rocha 2015[77]	4(4)	None	Pharmacy	Adherence	Neutral	Design	Low
Rueda 2006[78]	19(19)	MSM, ACB, PWID, Immigrants	Diverse	Adherence	Positive	Outcome, Design	Low
Ruzagira 2017[79]	14(3)	ACB	Peer or community based	Initiation	Neutral	Design	Low
Saberi 2011[80]	36(3)	None	Digital	Adherence	Positive	Intervention	Low
Saberi 2012[81]	32(2)	MSM, ACB	Pharmacy	Adherence	Positive	Intervention	Low
Scott-Sheldon 2017[82]	21(21)	ACB	Diverse	Adherence	Positive	Intervention	Low
Sharma 2016[83]	126(6)	MSM, ACB	Peer or community based	Retention	Positive		Low
Shaw 2016[84]	10(3)	MSM, ACB	Diverse	Adherence	Positive	Population, Design	High
Suthar 2017[85]	4(1)	ACB	Economic	Retention	Positive	Evidence	Low
Swann 2018[86]	38(9)	ACB, PWID	Economic	Retention	Positive	Evidence, Design	High
Tang 2015[87]	21(5)	ACB	Diverse	Retention	Indeterminate	Evidence, Intervention	High
van Camp 2013[88]	10(7)	ACB	Task shifting	Adherence	Positive	Design	Unclear

van der Heijden 2017[89]	16(19)	MSM, ACB	Behavioral	Adherence	Neutral	Evidence, Population	Low
van Velthoven 2012[90]	9(9)	PWID	Digital	Adherence	Neutral	Population	Low
van Velthoven 2013[91]	21(4)	ACB	Digital	Adherence	Neutral	Design	High
Vervloet 2012[92]	13(5)	None	Digital	Adherence	Positive	Population, Intervention	Low
Vojnov 2016[93]	30(3)	ACB	Health system	Initiation	Positive	Evidence	Low
Wise 2008[94]	21(8)	None	Digital	Adherence	Indeterminate	Evidence, Design	High
Wouters 2012[95]	29(7)	ACB	Peer or community based	Adherence	Positive	Design	Unclear
Wynberg 2014[96]	15(1)	ACB, Immigrants	Health system	Retention	Neutral	Intervention	Low
Yang 2014[97]	11(11)	None	Diverse	Adherence	Positive	Design	Unclear
Young 2010[98]	13(13)	ACB	Peer or community based	Retention	Positive	Evidence, Population	Low

ACB: African, Caribbean and Black people; CSW: commercial sex workers; MSM: men who have sex with men; PWID: people who inject drugs; RCTs: randomized controlled trials; RoB: risk of bias.

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Supplement 3: List of excluded studies

Not a systematic review:

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An overview of systematic reviews on strategies to improve treatment initiation, adherence to antiretroviral therapy and retention in care for people living with HIV: part 1

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An overview of systematic reviews on strategies to improve treatment initiation, adherence to antiretroviral therapy and retention in care for people living with HIV: part 1

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Abstract

Objectives:

We sought to identify effective pragmatic interventions that increase initiation of antiretroviral therapy, adherence to antiretroviral therapy and retention in care for people living with HIV at high risk for poor engagement in care.

Methods:

We conducted an overview of systematic reviews of trials on interventions which target improved initiation of antiretroviral therapy, adherence to antiretroviral therapy and retention in care among people of higher risk of low engagement (men who have sex with men, African, Caribbean and Black people, sex workers, people who inject drugs, indigenous peoples and other socially marginalised groups). We searched PubMed, EMBASE, CINAHL, PsycINFO, Web of Science and the Cochrane Library in November 2018. We screened, extracted data and assessed methodological quality in duplicate and present a narrative synthesis.

Results:

We identified 2420 records of which only 98 systematic reviews were eligible. Overall, 65/98 (66.3%) were at low risk of bias. Systematic reviews focused on African, Caribbean and Black (66/98; 67.3%), men who have sex with men (32/98; 32.7%), people who inject drugs (6/98; 6.1%), sex workers and prisoners (both 4/98; 4.1%). Interventions were: mixed (37/98; 37.8%), digital (22/98; 22.4%), behavioral or educational (9/98; 9.2%), peer or community-based (8/98; 8.2%), health system (7/98; 7.1%), medication modification (6/98; 6.1%), economic (4/98; 4.1%), pharmacy based (3/98; 3.1%),or task-shifting (2/98; 2.0%). Most of the reviews concluded that the interventions worked (69/98; 70.4%), 17.3% (17/98) were neutral or were indeterminate12.2% (12/98). Knowledge gaps were the types of participants included in primary studies (vulnerable populations not included), poor research quality of primary studies and poorly tailored interventions (not designed for vulnerable populations). Digital, mixed and peer/community-based interventions were reported to be effective across the continuum of care.

Conclusions:

Interventions along the care cascade are mostly focused on adherence and do not sufficiently address all vulnerable populations.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To the best of our knowledge, this is the first overview to address the whole cascade of care for people living with HIV
- Our categorization of systematic reviews by intervention type and the intervention's success will permit decision makers to easily identify the interventions that are likely to work for their specific context
- We categorized systematic reviews to facilitate data synthesis, however we acknowledge that certain interventions may fit into multiple categories
- Among mixed interventions, it was challenging to determine the role of the individual intervention types on the overall effect
- This report at the systematic review level does not cover all aspects of the interventions, which can only be retrieved from individual trials

Background

Despite advances in diagnosis and management of HIV infection, many people living with HIV still do not have optimal outcomes. In 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDS) set the 90-90-90 target for 2020.[1] If this target is met, 90% of people living with HIV will know their HIV status; 90% of all people diagnosed with HIV will be receiving antiretroviral therapy (ART) and 90% of all people on ART will be virally suppressed.[1] These targets are contingent on engagement in the cascade of care that includes access to testing, timely diagnosis, access to and initiation of treatment, adherence to treatment and retention in care. Despite national efforts, very few countries have actually met these targets.[2] The UK has met these targets[3] and Botswana and Australia are on track.[4] Canada is also on track to meet these targets, with 87% of people with HIV diagnosed, 82% on treatment and 93% virally suppressed.[5] For countries to meet these targets, there must be policies in place to support programs that deliver interventions across the entire cascade of care. As such, there must be awareness, reductions in stigma and incentives that promote testing alongside strategies to enhance treatment initiation, adherence and retention in care. [6] Consistent access to ART and high-quality data should be collected so that advances towards the targets can be measured appropriately.[6]

If all these conditions are met and countries meet these targets, there are still concerns that the targets may be met at a national level but not in certain sub-populations. [7,8] The literature suggests that vulnerable populations such as men who have sex with men (MSM), sex workers (SW), people who inject drug (IDU), people with precarious migration status and ethno-racial minorities have a higher disease burden, worse engagement in care and are less likely to achieve viral suppression.[9-14] MSM and SWs all over the worlds are 19 and 13.5 times more likely to be living with HIV.[7,8] In Canada, inequities in social and structural determinants such as injection drug use, ethno-racial background, age, housing, sex work and gender affect engagement in care.[11-15]

The literature is rife with interventions aimed at improving different aspects of the care cascade. However, the challenges countries face in achieving the UNAIDS targets suggests that the interventions may not be effective, may not be properly translated into practice, or may not be tailored (designed to have optimal impact on groups with different sociodemographic or risk characteristics that could influence the effect of the intervention) to the relevant populations. Therefore, due consideration of the settings in which interventions are tested, their target populations, complexity and applicability in the real world are important considerations for scale up.[16,17] These limitations in the quality and quantity of evidence were identified in the International Association of Physicians in AIDS Care (IAPAC) guideline document.[18]

While HIV is still a leading cause of disease burden in sub-Saharan Africa,[19] vulnerable populations in high income countries may experience a comparable disease burden if they are not recognised as a priority.[20] As countries strive to meet the 90-90-90 targets, it is becoming apparent that due to the disparities in outcomes across jurisdictions and populations, better targeted approaches are required to improve engagement in care.[21] Ontario is the most populous province of Canada and home to 42% of Canada's 71000 people living with HIV. Due to individual, social and structural factors, it is estimated that approximately 20% of these people living with HIV in Canada have discontinuous care.[11] In Ontario, 80-87% of people living with HIV are in care, 70-82% are on ART and 67-81% are virally suppressed.[22] This overview of systematic reviews will inform policy, practice and research in Ontario and other high-income settings especially with regards to engagement in HIV care for vulnerable populations. We sought to summarise the available evidence on strategies that improve engagement in the HIV care cascade (initiation of treatment, adherence to medication and retention in care) for priority populations in high income countries and as well as to identify knowledge gaps. See figure 1.

This overview is the first part of our report and includes a high-level summary of the findings from systematic reviews, with no distinction by country. The second part will summarise the findings from the randomized trials included in the systematic reviews.

Figure 1: Outline of the HIV care cascade

Methods

We conducted an overview of systematic reviews using standard Cochrane methods.[23] The protocol for this overview has been published elsewhere.[24] Key features of our methods are outlined below.

Patient and public involvement:

Our research question was formulated and refined based on input from the Ontario HIV Treatment Network (OHTN), a non-profit network, as part of their strategy to close gaps in the cascade of care for key populations. The investigators include patients, clinicians, researchers and representatives of AIDS Service Organizations/Community-Based Organizations (ASO/CBOs). Decision makers and representatives from the Ministry of Health and Long-Term Care (MOHLTC) of Ontario were also consulted.

Criteria for considering reviews for inclusion

We included any systematic reviews with at least one study with a randomized comparison of an intervention designed to improve initiation of ART, adherence to ART and/or retention in care among people living with HIV. We excluded abstracts, non-systematic reviews and other overviews. All comparators (e.g. attention control, usual care, another intervention etc.) were eligible for inclusion.

Search methods for identification of reviews

We conducted an exhaustive and comprehensive search of the following databases: PubMed, EMBASE (Exerpta Medica Database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), PsycINFO, Web of Science and the Cochrane Library; from1995 (when combination ART was introduced) to 13 November 2018. The search strategy was reviewed by a Librarian at Health Sciences Centre Library at McMaster University. The full search strategy is reported as a supplementary file (online supplementary appendix 1).

We also searched the websites of the World Health Organization (WHO), United Nations Programme on HIV/AIDS (UNAIDS), National Institute for Health and Care Excellence (NICE) and the systematic review database housed at the Ontario HIV Treatment Network (OHTN): Synthesized HIV/AIDS Research Evidence (SHARE; http://www.hivevidence.ca/frmSearch.aspx).

Finally, we looked for additional systematic reviews in the bibliographies of the included reviews.

Screening

The results of our search were collated in EndNote reference manager.[25] Duplicates were removed and all the references were uploaded unto DistillerSR (Evidence Partners, Ottawa, Canada). We screened the retrieved citations in duplicate with reviewer pairs (BZ, AW, AH) first by examining the titles and abstracts and secondly by examining the full texts. Systematic reviews that met our inclusion criteria were processed and data were extracted.

Data items

From the systematic reviews, we extracted standard bibliometric data (author, year), number of included primary studies and their designs, target populations, types of interventions, outcomes of interest, key findings and knowledge gaps. Data were extracted in duplicate by reviewers working in pairs (BZ, AW, AH).

Assessment of methodological quality of included reviews

We appraised the methodological quality of the included reviews using the risk of bias in systematic reviews (ROBIS) tool.[26] This tool allows reviewers to assess the relevance of the question, identify concerns with the review process and make a judgement on risk of bias (high, low, unclear). Risk of bias was appraised in duplicate by pairs of reviewers (BZ, AW, AH).

Discrepancies and disagreements in screening, data extraction and risk of bias were resolved by consensus or by adjudication by a third reviewer (LM).

Data synthesis

The extracted data were described narratively. Systematic reviews were organised according to the portion of the care cascade they addressed (i.e. initiation, adherence, retention) and the intervention types: behavioral or educational, digital, mixed, economic, health system, medication modification, peer or community-based, pharmacy based or task-shifting. These categories were developed post-hoc to facilitate data synthesis. The types of interventions included in each category are outlined in Table 1.

Table 1: Categorization of intervention types in the systematic reviews

Intervention category	Types
Behavioral & Educational	Medication-assisted therapy, mindfulness-based stress reduction, motivational interviewing, psychotherapy, relaxation
Digital	Digital technology-based interventions such as alarms, electronic pillboxes, and pagers, mobile device text messages and voice messages, computer-based or internet-based interventions, online support communities and electronic medication packaging
Mixed	Combinations of any of the listed categories
Economic	Food assistance, cash incentives, performance-based financing, household economic strengthening
Health system	Point of care services, decentralised services, less frequent visits
Medication modification	Single tablet regimens, fixed dose combinations, rapid medication initiation, observed therapy
Peer or community-based	Home-base care, community-based services including the use of community health workers, lay health workers, treatment buddies, field officers, peer educators, volunteers and counsellors.
Pharmacy-based	Changes to standard pharmacy service delivery, pharmacist delivered interventions
Task-shifting	Service delivery by non-doctor staff, nurse-led interventions

Conclusion statements were categorized according to a previously used framework: positive (evidence of effectiveness); neutral (no evidence of effectiveness or no opinion); negative (authors advise against the use of intervention); indeterminate (insufficient evidence or more research is required).[27] Knowledge gaps were operationalised according to guidance on how to report research recommendations by identifying the state of the evidence, participants, interventions, comparisons and outcomes for which further research is needed.[28] We also discuss our findings within the scope of the Health Systems Arrangement Framework. [29] In this framework, interventions may be organized to inform different parts of the decision-making process, and interventions can be related to governance, financial or delivery arrangements. [29] Interventions effects are summarised according to the vulnerable population they were tested with,

intervention target (initiation, adherence, retention) and risk of bias. Interventions reported in systematic with positive recommendations are highlighted. Our findings are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [30]

Results

Literature search:

Our search identified 2,420 records from electronic databases and 76 from other sources. After removal of duplicates, 1505 titles and abstracts were screened, of which 1006 were considered ineligible and excluded. We further screened 499 full text articles and included 98. Agreement on the screening of full text articles was high (Kappa=0.79). The screening process is outlined in a PRISMA flow diagram (Figure 2).[30] A full list of excluded systematic reviews is provided as a supplementary file (online supplementary appendix 2)..

Figure 2: Systematic review flow diagram

Description of included reviews

The 98 included systematic reviews were published between 2006 and 2018[31-128] and reported on interventions to improve initiation of care (n=18),[32,41,54,58,61,64,65,70,75,78,81,84,92,100,109,113,123,126] adherence to ART (n=82)[31-36,38,39,41-53,55,57,59,60,62,65-68,71-77,79-108,110-112,114-116,118-122,124,125,127,128] and retention in care (n=39).[32,37,40,41,52,56,58-60,63-66,68-70,75-78,81,84,86,88,89,91-93,95,96,100,101,105,113,115-117,126,128] Thirty-one (31) reviews reported two or more aspects of the cascade.[32,41,52,58-60,64-66,70,75-78,81,84,86,88,89,91,92,95,96,100,101,105,113,115,116,126,128] They included a median (quartile 1; quartile 3 [Q1; Q3]) of 19 (11;28) primary studies and 8(4;13) randomized trials.

With regards to vulnerable populations, 32.7% (32/98) included primary studies involving MSM,[31,33,40-42,45,47,48,51,52,59,65,70,73,80,81,85,87,89,92,96,98-100,104-106,108,110,113,114,119] 67.3% (66/96) involving African, Caribbean or Black People,[31-34,36,37,40,43,45,47,48,50,52-54,56,58-61,63-66,70,71,73-82,84-87,89,90,92,93,95,101-104,106,108-110,112-120,123,125,126,128] 25.5% (25/98) focused on PWID,[39,41,43,44,48,50-52,60,66,68,70,73,74,85,88,91,92,96,99,100,105,108,116,121] 6.1% (6/98) involving SW,[41,42,48,52,96,100] 4.1% (4/98) included data on immigrants, [42,82,108,126] and 4.1% (4/98) included data on incarcerated persons.[40,60,91,105] These characteristics are summarised in table 2. A full list of the 98 included systematic reviews is reported as a supplemental file (online supplementary appendix 3).

Table 2: Summary characteristics of included systematic reviews: n=98

Variable	Statistic
Year: median (quartile 1; quartile 3)	2015 (2013;2017)
Number of included primary studies: median (quartile 1; quartile 3)	29 (11; 28)
Number of randomized trials: median (quartile 1; quartile 3)	8 (4;13)
Vulnerable populations included: n (%)	
African, Caribbean or Black	66 (67.3)
Men who have sex with men	32 (32.7)
People who inject drugs	25 (25.5)
Sex workers	6 (6.1)
Immigrants	4 (4.1)

Incarcerated persons	4 (4.1)
Intervention categories: n (%)	
Mixed	37 (37.8)
Digital	22 (22.4)
Behavioral or educational	9 (9.2)
Peer or community based	8 (8.2)
Health system	7 (7.1)
Medication modification	6 (6.1)
Economic	4 (4.1)
Pharmacy	3 (3.1)
Task shifting	2 (2.0)
Care cascade outcomes: n (%) *	
Adherence	82 (59.0)
Retention	39 (28.1)
Initiation	18 (12.9)

*not mutually exclusive

Methodological quality of included reviews

Most of the systematic reviews were judged to be a low risk of bias (65 [66.3%]). Twenty (20.4%) were judged to be at high risk of bias and 13 (13.3%) were judged to be at unclear risk of bias. The most frequent concern was related to data collection and primary study appraisal (28.6% at high risk of bias in this domain). The main concerns we identified were no risk of bias assessments conducted, missing primary study information and no evidence that data had been processed in duplicate. This was followed by the risk of bias in the identification and selection of primary studies (19.4% at high risk of bias in this domain). The main limitations we identified were not searching grey literature, searching less than 2 databases, exclusion of non-English primary studies, no evidence that data were processed in duplicate and not reporting the search strategy. For the domain of study eligibility criteria (15.3% at high risk of bias in this domain) the main concerns were: eligibility criteria not described in sufficient detail, ambiguous criteria and restrictions based on publication status and language. For the domain of synthesis and findings (15.3% at high risk of bias in this domain) the main concerns were: heterogeneity was not assessed, choice of synthesis approach not justified and primary study biases not addressed. See figure 3 and online supplementary appendix 3.

Figure 3: Risk of bias summary

Effects of interventions

Most systematic reviews gave positive recommendations for the interventions they examined (69/70.4%). Seventeen (17.3%) were neutral and 12 (12.2%) were indeterminate. No systematic reviews recommended against any interventions. Positive findings from systematic reviews are outlined below. All our findings, positive, negative, neutral and indeterminate are summarised in a supplementary file (online supplementary appendix 3).

Initiation

Of the 18 systematic reviews that examined initiation of ART as an outcome, 11 (61.1%) at low risk of bias reported that digital,[41,100] mixed,[32,54,75,84] health system [66,78,123] and peer or community-based interventions [65,113] improved initiation of ART. Two systematic reviews at high or unclear risk of bias reported that digital,[64] and mixed interventions improved initiation of ART.[70]

Adherence

Of the 82 systematic reviews that examined adherence to ART as an outcome, 25 (30.5%) at low risk of bias reported that behavioral/educational,[44,45] digital,[31,33,41,46,52,79,98,100,101,111,122] mixed,[32,36,43,53,57,62,72,74,75,82,84,91,103,105,108,112] health system,[50] medication modification,[49,59,102] peer/community-based,[73,96,128] pharmacy[86,111] and task-shifting interventions[77] improved adherence to ART. Eighteen (18/21.9%) systematic reviews at high or unclear risk of bias reported that behavioral/educational,[39,104] digital,[42,71,85,90] mixed,[50,80,89,99,114,127] economic,[55,68,116] medication modification,[97] peer or community-based[125] and task-shifting [118]interventions improved adherence to ART.

Retention

Of the 39 systematic reviews that examined retention in care as an outcome, 21 (53.8%) systematic reviews at low risk of bias reported that digital,[41,52,100] mixed,[32,66,69,75,84,91,105] economic,[115] health system,[66,78,95] medication modification,[59] peer/community-based[65,96,113,128] and task shifting[77] interventions improved adherence to HIV care. Seven (7/17.9%) of systematic reviews at high or unclear risk of bias reported that behavioral/educational,[37] digital,[64] mixed,[70,89] economics,[116] health system[40] and peer or community-based interventions[56] improved retention in care.

Knowledge gaps

The most frequent knowledge gap identified in 22 (22.4%) systematic reviews was with regards to the population studied, where further investigation with vulnerable and marginalized groups such as children, youth, MSM, pregnant and breast-feeding women, individuals in low-income settings, individuals with concurrent mental health issues and older adults is required. The authors also raised concerns about the primary study designs (n=22/22.4%), and primarily called for more robust, innovative, rigorous and high-quality designs, including experimental designs, (pragmatic) randomized trials, longer follow-up times, mixed methods approaches, and primary studies with larger sample sizes. The nature of the intervention was also identified as a knowledge gap (22/22.4%). The authors found that interventions were not sufficiently tailored to high-risk populations, low-income settings, were too costly or didn't cover the entire cascade of care. They further suggested that novel interventions be investigated, and older intervention be combined to assess synergistic effects. Only two (2.0%) systematic reviews raised concerns about the nature of the outcomes used.[72,83] They called for universal definitions for adherence and the use of more humanistic, economic and patient-important outcomes.

Discussion

We conducted an exhaustive and comprehensive search for systematic reviews focused on examining interventions that enhance ART initiation, ART adherence and retention among people living with HIV. We included 98 systematic reviews. Most of the systematic reviews we identified focused on adherence enhancing interventions and investigated a mixed range of intervention categories. For the most part, the authors of the included systematic reviews found that the interventions were effective (70.4%). Digital, mixed and peer/community interventions were the only three categories of interventions that were reported to be effective across the whole continuum of care. The main knowledge gaps identified in most systematic reviews was a lack of focus on the populations that would benefit the most (22.4%), poor quality of the primary studies (22.4%) and nature of the interventions. (22.4%).

We further examined to what extent health systems arrangements were met by this body of evidence. Most systematic reviews focused on the delivery of interventions (task-shifting, homebased care, pharmacy-based interventions etc.) but none addressed governance of HIV care and very few addressed financial components (food assistance, cash incentives, performance-based financing, household economic

strengthening) that may support or hinder access to HIV care and treatment. [55,68,115,116] This may be an important limitation in how research is designed, without adequate consideration of the facets of a health system that could influence outcomes.

Most of the systematic reviews were at low risk of bias (66.3%).[26] However, there were some concerns, notably with issues related to reporting of details in review conduct which indicated high or unclear risk of bias. We recognise that journal word count limitations may prevent authors from reporting all the relevant details, but appendices could be used to provide additional details. Risk of bias from these systematic reviews should be interpreted in context and may differ from the risk of bias in the primary studies included.

To the best of our knowledge, there is no other overview of systematic reviews investigating the cascade of HIV care, but our findings confirm previous research indicating a paucity of research on vulnerable populations,[129] and challenges with scaling-up interventions.[130]

The disproportionate study of adherence might be due to it's perceived importance as a cornerstone of care, or the relative ease of designing adherence studies. Prior to recent recommendations to treat all diagnosed people, initiation of treatment was seldom a priority. [131]Likewise, retention in care is an outcome that requires substantially longer follow up to generate meaningful results.[11,132] In order for countries to meet the 90-90-90 target, the cascade of care must be viewed as continuum, not just for practice, but also for research, such that interventions that strengthen the entire cascade be scaled up.

Even though only disparate definitions of adherence to ART were identified by the authors of some systematic reviews, we believe such diversity may exist with retention in care, as other studies have noted that there is no gold standard for what constitutes adequate retention. [133] Future work on the trials included in the systematic reviews will permit us the describe the breadth of definitions used for both adherence and retention. Standardized definitions are important for jurisdictions to be able to measure changes over time and make cross jurisdictional comparisons. Standardized definitions will also help systematic reviewers to synthesize research.

Strengths and limitations:

We acknowledge the following limitations. Despite our attempt to group the interventions into categories, we recognise that certain interventions may fit into more than one category. For example, tasking shifting and pharmacy-based interventions can be viewed as health system or community based interventions. Secondly, for the group of systematic reviews that investigated mixed interventions, it is challenging to determine the role of the individual intervention types on the overall effect. This group could contain interventions from any category and therefore it is not surprising that the systematic reviews that included mixed interventions often found a significant effect. Within each systematic review, the diversity of study designs, populations and primary studies from various income levels precluded in-depth investigation of how these issues may have affected intervention effectiveness at the systematic review level. No distinction was made between ACB populations in their respective countries versus ACB populations in high income countries where the vulnerability is different. Further ongoing work on the trials included in these systematic reviews will highlight the features of interventions in ACB populations. Some primary studies are included in more than one systematic review. This highlights the need for a primary study-level analysis. Finally, despite our efforts to conduct a comprehensive and exhaustive search, it is possible that some systematic reviews were missed if they were indexed with terms we did not include in our strategy.

This work has many strengths. In addition to using a predefined protocol, we conducted a comprehensive search, assessed risk of bias, investigated the availability of data on vulnerable populations and categorised the systematic reviews by type of intervention and success of the intervention. This approach would permit decision makers and other end users to identify intervention type that are likely to work for specific

populations at each point of the care cascade. However, a trial-level analyses is required to enrichen these findings.

Conclusion:

We found limited research on vulnerable populations and uneven focus on the three aspects of the care cascade. In order to identify the most effective and pragmatic interventions for vulnerable populations in high income settings, a study-level analysis is required. The diversity of the interventions examined and the populations studied indicate the need for network meta-analyses in this field, some of which have already been published.[90] The lack of systematic reviews that generate evidence on governance is indicative of how removed many research endeavours are from policy-making. Monitoring and evaluation also need to be considered within systems to support up-to-date collection of data on detection, initiation, adherence and retention in care.

Differences between protocol and review

There are a few differences between this report and the protocol. First, after additional consultation with stakeholders we included interventions targeting initiation of ART. Given the amount of data, we decided to report our findings on two levels, the systematic review level and the primary study level. Only the systematic review level is reported here, and therefore in-depth analyses of the settings (high versus low income) of the primary studies and the levels of pragmatism, and certainty of the evidence are reserved for a second paper.

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Authors contributions

LM developed the first draft of the manuscript. AH, AW, LM, BZ extracted data and created tables. EA, DOL, BR, MS, DM, LPR, CL, SM, AB, WH, AH, AW, BZ and LT revised several versions of the manuscript and approved the final version. LM is the guarantor of the manuscript.

Declarations of interest

The authors declare none.

Data availability

All data relevant to the study are included in the article or uploaded as supplementary information

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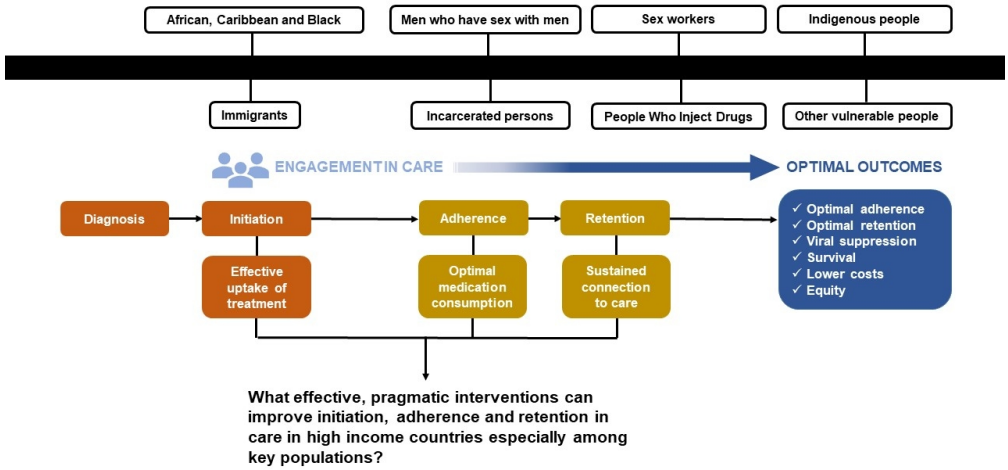

Figure 1: Outline of the HIV care cascade

108x60mm (300 x 300 DPI)

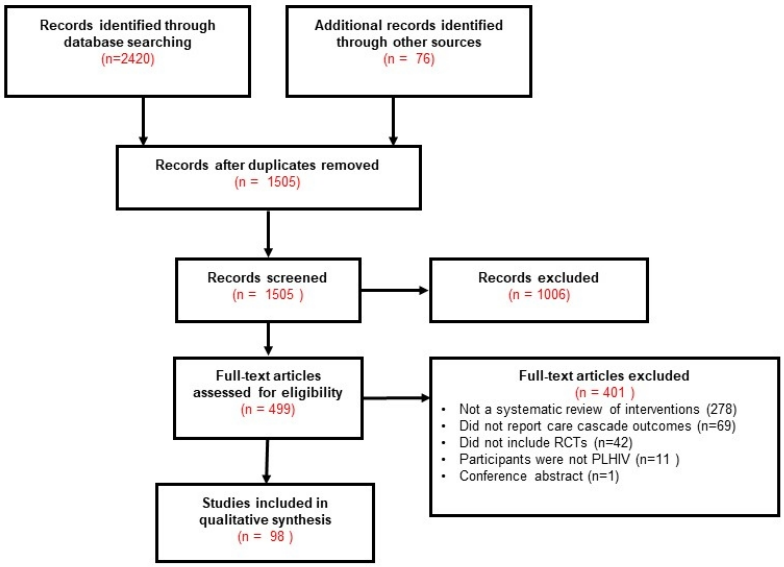

Figure 2: Systematic review flow diagram

81x60mm (300 x 300 DPI)

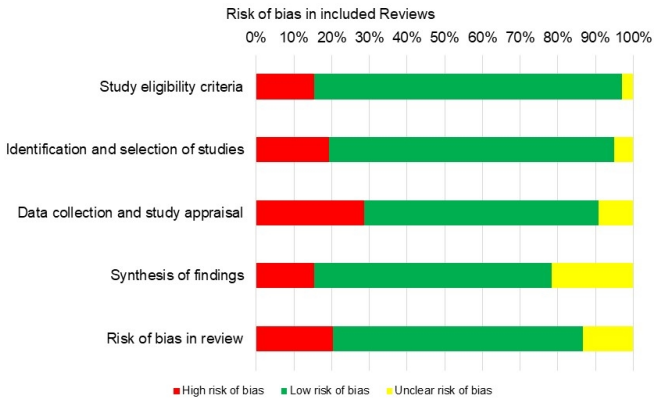

Figure 3: Risk of bias summary

108x60mm (300 x 300 DPI)

Supplement 1: Search strategy

November 12 & 13, 2018: N = 2420

DATABASES:
CINAHL, N = 195 (Nov-13)
Cochrane Library of Systematic Reviews, N = 217 (Nov-13)
Embase, N = 947 (Nov-12)
PsycINFO, N = 105 (Nov-12)
PubMed, N = 304 (Nov-13)
Web of Science, N = 652 (Nov-13)

SEARCH METHODS (as per protocol manuscript):

- From 1995 to present (when combination ART was introduced), no language restrictions: Systematic review OR meta-analysis
+ Adhere*~~nce~~ OR complian*~~ce~~ OR retention OR dropout~~s~~ OR los*~~s~~ adj2 to follow-up OR attrition OR nonadheren* OR uncompliant~~t~~* OR treatment refusal OR persistence OR ~~non-persistence~~ OR initiat* OR start* OR uptake
+ HIV OR human immune-deficiency virus OR human immuno-deficiency virus
+ Antiretroviral therapy OR antiretrovirals OR antiretroviral treatment OR Highly Active Antiretroviral Therapy OR ART or HAART

Librarian Consult (November 12, 2018)
Q: Verify adequate capture of HIV SRs

- impossible to get MeSH for all keywords but make sure to get good subject headings for the main concepts at the very least (e.g. antiretroviral treatment, HIV)
- fix truncated terms ‘adherence’, ‘uncompliant*’
- could add adj2 for los* to follow-up
- good practice to use explode throughout

Q: Verify CINAHL searching

- doesn’t use MeSH, need to look up subject headings (uncheck box to get the key word)
- re: WoS – use ‘SU’ to ~ represent search in all fields

Database: CINAHL via EBSCOhost Research Databases
Completed on: November 13, 2018
Search Strategy:

S1	(MH "Systematic Review")	68,246
S2	(MH "Meta Analysis")	35,345
S3	S1 OR S2	87,072
S4	(MH "Patient Compliance+") OR (MH "Treatment Refusal") OR (MH "Medication Compliance")	46,042
S5	(MH "Research Subject Retention")	692
S6	(MH "Research Dropouts") OR (MH "Patient Dropouts")	2,506
S7	(MH "After Care")	11,133
S8	adhere* OR nonadhere* OR complian* OR uncomplian* OR retention OR dropout OR lost to follow-up OR attrition OR treatment refusal OR persistence OR non-persistence OR initiat* OR start* OR uptake	339,844
S9	S4 OR S5 OR S6 OR S7 OR S8	349,538
S10	(MH "Human Immunodeficiency Virus+")	8,168
S11	(MH "HIV-Infected Patients+") OR (MH "HIV Infections+")	80,662
S12	HIV OR human immun* deficiency virus	96,874
S13	S10 OR S11 OR S12	104,864
S14	(MH "Antiretroviral Therapy, Highly Active")	5,519
S16	antiretroviral therapy OR antiretrovirals OR antiretroviral treatment OR anti-HIV agents OR anti-retroviral agents OR Highly Active Antiretroviral Therapy OR HAART	24,400
S17	S14 OR S15 OR S16	26,013
S18	S3 AND S9 AND S13 AND S17	**195**

(Limiter: Published Date: 19950101-20181231)
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Database: Cochrane Database of Systematic Reviews
Completed on: November 13, 2018 (updated search from 216 results on Nov-7)
Search Strategy:

'systematic review OR meta-analysis in All Text AND adherence OR compliance OR retention OR dropouts OR loss to follow-up OR attrition OR nonadheren* OR uncompliant* OR treatment refusal OR persistence OR non-persistence OR initiat* OR start* OR uptake in All Text AND HIV OR human immune-deficiency virus OR human immuno-deficiency virus in All Text AND antiretroviral therapy OR antiretrovirals OR antiretroviral treatment OR Highly Active Antiretroviral Therapy OR ART or HAART in All Text - with Cochrane Library publication date Between Jan 1995 and Dec 2018 (Word variations have been searched)' (216)

'adhere* OR nonadhere* OR complian* OR uncomplian* OR retention OR dropout OR lost to follow-up OR attrition OR treatment refusal OR persistence OR non-persistence OR initiat* OR start* OR uptake in All Text AND HIV OR human immun* adj2 deficiency virus in All Text AND antiretroviral therapy OR antiretrovirals OR antiretroviral treatment OR anti-HIV agents OR anti-retroviral agents OR Highly Active Antiretroviral Therapy OR ART OR HAART in All Text - with Cochrane Library publication date Between Jan 1995 and Dec 2018 (Word variations have been searched)' **(217)**
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Database: Embase <1974 to 2018 November 09> via Ovid
Completed on: November 12, 2018 (updated search from 720 results on Nov-7)
Search Strategy:

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1 systematic review.mp. or exp "systematic review"/ (241913)
2 meta analysis.mp. or exp "meta analysis"/ (232198)
3 (complian* or uncomplian*).mp. or exp "medication compliance"/ (306191)
4 retention.mp. (225178)
5 dropout.mp. or exp "patient dropout"/ (10447)
6 (los* adj2 to follow up).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (35898)
7 attrition.mp. (14277)
8 (adhere* or nonadhere*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (255209)
9 treatment refus*.mp. or exp "treatment refusal"/ (17490)
10 persistence.mp. (102883)
11 initiat*.mp. (789288)
12 start*.mp. (634133)
13 uptake.mp. (461506)
14 1 or 2 (366337)
15 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (2578956)
16 (HIV or human immune-deficiency virus or human immuno-deficiency virus).mp. (367212)
17 exp "human immunodeficiency virus"/ or exp "human immunodeficiency virus infection"/ or exp "human immunodeficiency virus infected patient"/ (452990)
18 16 or 17 (501218)
19 antiretroviral therapy.mp. or exp "antiretroviral therapy"/ (69407)
20 antiretrovirals.mp. (4928)
21 antiretroviral treatment.mp. (9740)
22 exp "antiretrovirus agent"/ (178047)
23 highly active antiretroviral therapy.mp. or exp "highly active antiretroviral therapy"/ (38980)
24 (ART or HAART).mp. (170581)
25 19 or 20 or 21 or 22 or 23 or 24 (340645)
26 14 and 15 and 18 and 25 (948)
27 limit 26 to yr="1995 -Current" **(947)**

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Database: PsycINFO <1987 to November Week 1 2018> via Ovid
Completed on: November 12, 2018 (updated search from 101 results on Nov-7)
Search Strategy:

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1 systematic review.mp. (21950)
2 meta analysis.mp. or exp "meta analysis"/ (25527)
3 1 or 2 (41919)
4 exp "compliance"/ or exp "treatment compliance"/ (16310)
5 (complian* or uncomplian*).mp. (32297)
6 dropout.mp. or exp "treatment dropout"/ (7191)
7 retention.mp. (34515)
8 attrition.mp. or exp "experimental attrition"/ (6818)
9 (los* adj2 to follow up).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (1103)
10 adhere*.mp. (31235)
11 treatment refus*.mp. or exp "treatment refusal"/ (886)
12 persistence.mp. (16819)
13 initiate.mp. (9915)
14 start*.mp. (82553)
15 uptake.mp. (13475)
16 nonadherence.mp. (1750)
17 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (215604)
18 HIV.mp. or exp "HIV"/ (52967)
19 (human immunodeficiency virus or human immune-deficiency virus or human immuno-deficiency virus).mp. (6071)
20 18 or 19 (53288)
21 exp "drug therapy"/ (121212)
22 (antiretroviral or antiretroviral therapy or antiretroviral treatment or ART or HAART).mp. (40678)
23 21 or 22 (158296)
24 3 and 17 and 20 and 23 (105)
25 limit 24 to yr="1995 -Current" **(105)**

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Database: PubMed <1995/01/01 to 31-Dec-2018>
Completed on: November 13, 2018 (updated search from 282 results on Nov-7)
Search Strategy:

((((((systematic review OR meta-analysis)) AND (adherence OR compliance OR retention OR dropouts OR loss to follow-up OR attrition OR nonadheren* OR uncompliant* OR treatment refusal OR persistence OR non-persistence OR initiat* OR start* OR uptake)) AND (HIV OR human immune-deficiency virus OR human immuno-deficiency virus)) AND (antiretroviral therapy OR antiretrovirals OR antiretroviral treatment OR Highly Active Antiretroviral Therapy OR ART or HAART)) AND systematic[sb]) AND systematic review[ti] (282)

((((((systematic review OR meta-analysis)) AND (adhere* OR nonadhere* OR complian* OR uncomplian* OR retention OR dropout OR lost to follow-up OR attrition OR treatment refusal OR persistence OR non-persistence OR initiat* OR start* OR uptake)) AND (HIV OR human immune-deficiency virus OR human immuno-deficiency virus)) AND (antiretroviral therapy OR antiretrovirals OR antiretroviral treatment OR Highly Active Antiretroviral Therapy OR ART OR HAART OR anti-HIV agents OR anti-retroviral agents)) AND systematic[sb]) AND systematic review[ti] Filters: Publication date from 1995/01/01 to 2018/12/31
(304)

MeSH headings [mh], captured via 'All Fields' search:
meta-analysis [publication type], meta-analysis as topic / review, systematic
patient dropouts / patient compliance (patient adherence/nonadherence) / treatment adherence and compliance (therapeutic adherence/compliance) / medication adherence (nonadherence, compliance/noncompliance) /lost to follow-up
HIV / anti-HIV agents / anti-retroviral agents / antiretroviral therapy, highly active (HAART)

systematic review	"review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "systematic review"[All Fields]
meta-analysis	"meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields]
retention	"retention (psychology)"[MeSH Terms] OR ("retention"[All Fields] AND "(psychology)"[All Fields]) OR "retention (psychology)"[All Fields] OR "retention"[All Fields]
lost to follow-up	"lost to follow-up"[MeSH Terms] OR ("lost"[All Fields] AND "follow-up"[All Fields]) OR "lost to follow-up"[All Fields] OR ("lost"[All Fields] AND "follow"[All Fields] AND "up"[All Fields]) OR "lost to follow up"[All Fields]
attrition	"tooth attrition"[MeSH Terms] OR ("tooth"[All Fields] AND "attrition"[All Fields]) OR "tooth attrition"[All Fields] OR "attrition"[All Fields]
treatment refusal	"treatment refusal"[MeSH Terms] OR ("treatment"[All Fields] AND "refusal"[All Fields]) OR "treatment refusal"[All Fields]
HIV	"hiv"[MeSH Terms] OR "hiv"[All Fields]
human	"humans"[MeSH Terms] OR "humans"[All Fields] OR "human"[All Fields]
immune-deficiency	"immunologic deficiency syndromes"[MeSH Terms] OR ("immunologic"[All Fields] AND "deficiency"[All Fields] AND "syndromes"[All Fields]) OR "immunologic deficiency syndromes"[All Fields] OR ("immune"[All Fields] AND "deficiency"[All Fields]) OR "immune deficiency"[All Fields]
virus	"viruses"[MeSH Terms] OR "viruses"[All Fields] OR "virus"[All Fields]
immuno-deficiency	"immunologic deficiency syndromes"[MeSH Terms] OR ("immunologic"[All Fields] AND "deficiency"[All Fields] AND "syndromes"[All Fields]) OR "immunologic deficiency syndromes"[All Fields] OR ("immuno"[All Fields] AND "deficiency"[All Fields]) OR "immuno deficiency"[All Fields]

therapy	"therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]
treatment	"therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]
Highly Active Antiretroviral Therapy	"antiretroviral therapy, highly active"[MeSH Terms] OR ("antiretroviral"[All Fields] AND "therapy"[All Fields] AND "highly"[All Fields] AND "active"[All Fields]) OR "highly active antiretroviral therapy"[All Fields] OR ("highly"[All Fields] AND "active"[All Fields] AND "antiretroviral"[All Fields] AND "therapy"[All Fields])
ART	"art"[MeSH Terms] OR "art"[All Fields]
HAART	"antiretroviral therapy, highly active"[MeSH Terms] OR ("antiretroviral"[All Fields] AND "therapy"[All Fields] AND "highly"[All Fields] AND "active"[All Fields]) OR "highly active antiretroviral therapy"[All Fields] OR "haart"[All Fields]
anti-HIV agents	"anti-hiv agents"[Pharmacological Action] OR "anti-hiv agents"[MeSH Terms] OR ("anti-hiv"[All Fields] AND "agents"[All Fields]) OR "anti-hiv agents"[All Fields] OR ("anti"[All Fields] AND "hiv"[All Fields] AND "agents"[All Fields]) OR "anti hiv agents"[All Fields]
anti-retroviral agents	"anti-retroviral agents"[Pharmacological Action] OR "anti-retroviral agents"[MeSH Terms] OR ("anti-retroviral"[All Fields] AND "agents"[All Fields]) OR "anti-retroviral agents"[All Fields] OR ("anti"[All Fields] AND "retroviral"[All Fields] AND "agents"[All Fields]) OR "anti retroviral agents"[All Fields]

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Database: Web of Science
Completed on: November 13, 2018
Search Strategy:

#1	TS=(systematic review OR meta-analysis)	271,168
#2	TS=(adhere* OR nonadhere* OR complian* OR uncomplian* OR retention OR dropout OR los* follow-up OR attrition OR treatment refusal OR persistence OR non-persistence OR initiat* OR start* OR uptake)	2,512,891
#3	TS=(HIV OR human immun* deficiency virus)	306,952
#4	TS=(antiretroviral therapy OR antiretrovirals OR antiretroviral treatment OR anti-HIV agents OR anti-retroviral agents OR ART OR Highly Active Antiretroviral Therapy OR HAART)	461,846
#5	#4 AND #3 AND #2 AND #1	**652**

(Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1995-2018)
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List of excluded studies

Not a systematic review:

1. Abdulrahman, S. A.,Rampal, L.,Othman, N.,Ibrahim, F.,Kadir Shahar, H.,Radhakrishnan, A. P.. Socioeconomic Predictors of Adherence Behavior Among HIV-Positive Patients Receiving Antiretroviral Therapy in Selangor, Malaysia. Asia Pac J Public Health. 2017. 29:304-314
2. Abuogi, L. L.,Smith, C.,McFarland, E. J.. Retention of HIV-Infected Children in the First 12 Months of Anti-Retroviral Therapy and Predictors of Attrition in Resource Limited Settings: A Systematic Review. Plos One. 2016. 11:#pages#
3. Aderomilehin, O.,Hanciles-Amu, A.,Ozoya, O. O.. Perspectives and Practice of HIV Disclosure to Children and Adolescents by Health-Care Providers and Caregivers in sub-Saharan Africa: A Systematic Review. Front Public Health. 2016. 4:166
4. Aidala, A. A.,Wilson, M. G.,Shubert, V.,Gogolishvili, D.,Globerman, J.,Rueda, S.,Bozack, A. K.,Caban, M.,Rourke, S. B.. Housing Status, Medical Care, and Health Outcomes Among People Living With HIV/AIDS: A Systematic Review. Am J Public Health. 2016. 106:e1-e23
5. Alcorn, James Samuel. Evaluating the appropriateness of dosing adjustments in the coadministration of maraviroc and CYP3A inhibitors: A literature review. HIV & AIDS Review. 2016. 15:122-126
6. Aldir, I.,Horta, A.,Serrado, M.. Single-tablet regimens in HIV: does it really make a difference?. Curr Med Res Opin. 2014. 30:89-97
7. Anglemyer, A.,Rutherford, G. W.,Horvath, T.,Baggaley, R. C.,Egger, M.,Siegfried, N.. Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples. Cochrane Database Syst Rev. 2013. 2013 (4) (no pagination):CD009153
8. Anonymous,. Meeting Abstracts - Academy of Managed Care Pharmacy Nexus 2018. Journal of Managed Care and Specialty Pharmacy. Conference: Academy of Managed Care Pharmacy Nexus, AMCP. 2018. 24:#pages#
9. Arevalo, Maria Teresa Varela,Torres, Isabel Cristina Salazar,Sanchez, Diego Correa. Adherencia al tratamiento en la infeccion por HIV/AIDS. Consideraciones teoricas y metodologicas para su abordaje. Adherencia al tratamiento en la infeccion por VIH/SIDA. Consideraciones teoricas y metodologicas para su abordaje.. 2008. 11:101-113
10. Assawasuwannakit, P.,Braund, R.,Duffull, S. B.. A model-based meta-analysis of the influence of factors that impact adherence to medications. J Clin Pharm Ther. 2015. 40:24-31
11. Astuti, N.,Maggiolo, F.. Single-Tablet Regimens in HIV Therapy. Infect Dis Ther. 2014. 3:1-17
12. Barbara, Castelnuovo,Reynolds, Steven J.. Optimizing Treatment Monitoring in Resource Limited Settings in the Era of Routine Viral Load Monitoring. Current Tropical Medicine Reports. 2017. 4:1-5
13. Baril, J. G.,Angel, J. B.,Gill, M. J.,Gathe, J.,Cahn, P.,van Wyk, J.,Walmsley, S.. Dual Therapy Treatment Strategies for the Management of Patients Infected with HIV: A Systematic Review of Current Evidence in ARV-Naive or ARV-Experienced, Virologically Suppressed Patients. PLoS One. 2016. 11:e0148231
14. Barlow-Mosha, L.,Musiime, V.,Davies, M. A.,Prendergast, A. J.,Musoke, P.,Siberry, G.,Penazzato, M.. Universal antiretroviral therapy for HIV-infected children: a review of the benefits and risks to consider during implementation. J Int AIDS Soc. 2017. 20:21552

15. Barnighausen, T.. The role of the health system in HIV treatment-as-prevention. AIDS. 2010. 24:2741-2
16. Barroso, J.,Leblanc, N. M.,Flores, D.. It's Not Just the Pills: A Qualitative Meta-Synthesis of HIV Antiretroviral Adherence Research. J Assoc Nurses AIDS Care. 2017. 28:462-478
17. Beckham, S. W.,Beyrer, C.,Luckow, P.,Doherty, M.,Negussie, E. K.,Baral, S. D.. Marked sex differences in all-cause mortality on antiretroviral therapy in low- and middle-income countries: a systematic review and meta-analysis. J Int AIDS Soc. 2016. 19:21106
18. Berg, C. J.,Michelson, S. E.,Safren, S. A.. Behavioral aspects of HIV care: adherence, depression, substance use, and HIV-transmission behaviors. Infect Dis Clin North Am. 2007. 21:181-200, x
19. Berhan, A.,Berhan, Y.. Virologic response to tipranavir-ritonavir or darunavir-ritonavir based regimens in antiretroviral therapy experienced HIV-1 patients: a meta-analysis and meta-regression of randomized controlled clinical trials. PLoS One. 2013. 8:e60814
20. Bernaud, Camille,Rodallec, Audrey,Morrier, Marine,Allavena, Clotilde,Perre, Philippe,Pineau, Solene,Jovelin, Thomas,Hall, Nolwenn,Pineau, Samuel,Andre-Garnier, Elisabeth,Raffi, Francois. P017: Low virologic failure on TDF/FTC/RPV in HIV-infected naïve and virologically suppressed patients with strict clinical selection and/or DNA genotyping. Journal of the International AIDS Society. 2015. 18:17-18
21. Bezabhe, W. M.,Chalmers, L.,Bereznicki, L. R.,Peterson, G. M.. Adherence to Antiretroviral Therapy and Virologic Failure: A Meta-Analysis. Medicine (Baltimore). 2016. 95:e3361
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29. Brown, Jennifer,Vanable,. Stress management interventions for HIV-infected individuals: review of recent intervention approaches and directions for future research. Neurobehavioral HIV Medicine. 2011. 3:95-106

30. Burch, L. S.,Smith, C. J.,Phillips, A. N.,Johnson, M. A.,Lampe, F. C.. Socioeconomic status and response to antiretroviral therapy in high-income countries: a literature review. AIDS. 2016. 30:1147-62
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Supplement 2: Characteristics of included studies

Study ID	Total studies (RCTs)	Key populations included	Intervention type	Target	Conclusion	Knowledge gaps	RoB
Amankwaa 2018[1]	13(13)	MSM, ACB	Digital	Adherence	Positive	Intervention	Low
Ambia 2016[2]	34(10)	ACB	Diverse	Initiation, Adherence, Retention	Positive, Positive, Positive	Design	Low
Anglada-Martinez 2015[3]	20(3)	MSM, ACB	Digital	Adherence	Positive	Design	Low
Arrivillaga 2013[4]	16(5)	ACB	Diverse	Adherence	Neutral	Population, Design	Unclear
Barnighausen 2011[5]	26(15)	ACB	Diverse	Adherence	Positive	Intervention	Low
Bateganya 2015[6]	20(1)	ACB	Behavioral	Retention	Positive	Population, Intervention	Unclear
Bhatta 2017[7]	28(28)	None	Diverse	Adherence	Neutral	Design	High
Bain-Brickley 2011[8]	4(2)	None	Diverse	Adherence	Neutral	Population	Low
Binford 2012[9]	45(15)	PWID	Behavioral	Adherence	Positive	Population	High
Brennan 2014[10]	5(5)	MSM, ACB	Health system	Retention	Positive	Design	High
Cao 2017[11]	26(8)	MSM, PWID, CSW	Digital	Initiation, Adherence, Retention	Positive, Positive, Positive	Population, Intervention	Low
Catalani 2013[12]	62(4)	MSM, Immigrants, CSW	Digital	Adherence	Positive	Evidence	High
Chaiyachati 2014[13]	124(19)	ACB, PWID	Diverse	Adherence	Positive	Population, Design	Low
Chang 2014[14]	12(9)	PWID	Behavioral	Adherence	Positive	Intervention, Design	Low
Charania 2014[15]	9(10)	MSM, ACB	Behavioral	Adherence	Positive	Evidence	Low
Checchi 2014[16]	37(34)	None	Digital	Adherence	Positive	Intervention, Design	Low
Cho 2017[17]	10(10)	MSM, ACB	Digital	Adherence	Indeterminate	Evidence, Outcome	Low

Claborn 2015[18]	10(6)	MSM, ACB, PWID, CSW	Digital	Adherence	Indeterminate	Intervention, Design	Low
Clay 2018[19]	63(34)	None	Medication modification	Adherence	Positive	Evidence	Low
Crepaz 2015[20]	15(15)	PWID	Health system	Adherence	Positive	Intervention	Low
Crepaz 2015[21]	15(8)	MSM, ACB, PWID	Diverse	Adherence	Positive	Evidence	High
Daher 2017[22]	99(38)	MSM, ACB, PWID, CSW	Digital	Adherence, Retention	Positive, Positive	Population	Low
de Bruin 2010[23]	20(18)	ACB	Diverse	Adherence	Positive	Comparison	Low
de Jongh 2016[24]	12(2)	ACB	Diverse	Initiation	Positive	Evidence	Low
de Pee 2014[25]	10(0)	None	Economic	Adherence	Positive	Population, Design	Unclear
Decroo 2013[26]	18(2)	ACB	Peer or community based	Retention	Positive	Evidence	Unclear
Demonceau 2013[27]	79(30)	None	Diverse	Adherence	Positive	Design	Low
Feyissa 2014[28]	3(1)	ACB	Health system	Initiation, Retention	Neutral, Neutral	Evidence	Low
Ford 2009[29]	12(12)	ACB, PWID	Medication modification	Adherence, Retention	Neutral, Neutral	Intervention	Low
Ford 2018[30]	22(4)	MSM, ACB	Medication modification	Adherence, Retention	Positive, Positive	Population	Low
Fox 2016[31]	22(10)	ACB	Diverse	Initiation	Neutral	Evidence	Low
Ganguli 2016[32]	64(8)	None	Diverse	Adherence	Positive	Intervention	Low
Gaston 2014[33]	13(4)	ACB	Diverse	Retention	Indeterminate	Evidence	High
Geldsetzer 2016[34]	10(4)	ACB	Digital	Initiation, Retention	Positive, Positive	Evidence, Population	High
Genberg 2016[35]	9(8)	MSM, ACB	Peer or community based	Initiation, Adherence, Retention	Positive, Neutral, Positive	Evidence, Intervention	Low

Govindasamy 2014[36]	24(5)	ACB, PWID	Diverse	Initiation, Adherence, Retention	Positive, Neutral, Positive	Design	Low
Hart 2010[37]	17(11)	None	Medication modification	Adherence	Neutral	Design	Low
Herrmann 2017[38]	23(3)	PWID	Economic	Adherence, Retention	Neutral	Evidence	High
Higa 2012[39]	13(4)	MSM, ACB, PWID	Diverse	Initiation, Retention	Positive	Intervention, Design	Unclear
Higa 2016[40]	10(9)	None	Diverse	Retention	Positive	Evidence	Low
Higgs 2014[41]	26(4)	ACB	Digital	Adherence	Positive	Evidence	Unclear
Hill 2012[42]	5(5)	None	Diverse	Adherence	Positive	Evidence, Outcome	Low
Kanters 2016[43]	22(22)	MSM, ACB, PWID	Peer or community based	Adherence	Positive	Evidence, Design	Low
Kanters 2017[44]	85(87)	ACB, PWID	Diverse	Adherence	Positive	Population, Intervention, Design	Low
Keane 2017[45]	13(3)	ACB	Diverse	Initiation, Adherence, Retention	Positive, Positive, Positive	Intervention	Low
Knight 2018[46]	8(5)	ACB	Diverse	Adherence, Retention	Indeterminate, Indeterminate	Evidence, Population	Unclear
Kredo 2013[47]	16(2)	ACB	Health system	Initiation, Retention	Positive, Positive	Design	Low
Kredo 2014[48]	10(4)	ACB	Task shifting	Initiation, Retention	Neutral, Positive	Population, Intervention, Design	Low
Lima 2016[49]	9(9)	ACB	Digital	Adherence	Positive	Intervention, Design	Low
Ma 2018[50]	23(9)	MSM, ACB	Diverse	Adherence	Positive	Design	High
MacPherson 2015[51]	11(3)	MSM, ACB	Diverse	Initiation, Adherence, Retention	Indeterminate, Indeterminate, Indeterminate	Population, Design	Low

Manias 2010[52]	46(9)	ACB, Immigrants	Diverse	Adherence	Positive	Intervention, Design	Low
Mathes 2013[53]	21(21)	None	Behavioral	Adherence	Neutral	Outcome, Design	Low
Mavegam 2017[54]	6(1)	ACB	Diverse	Initiation, Adherence, Retention	Positive, Positive, Positive	Evidence, Population	Low
Mayer 2017[55]	33(24)	MSM, ACB, PWID	Digital	Adherence	Positive	Population	High
Mbeye 2017[56]	3(3)	ACB	Pharmacy	Adherence, Retention	Positive, Indeterminate	Evidence, Population, Intervention	Low
Mbuagbaw 2012[57]	28(4)	PWID	Behavioral	Adherence, Retention	Indeterminate, Indeterminate	Evidence, Population	Low
Mbuagbaw 2015[58]	49(49)	MSM, ACB	Diverse	Adherence	Neutral	Population, Intervention, Design	Low
Medley 2015[59]	92(11)	MSM, ACB	Diverse	Adherence, Retention	Positive, Positive	Population, Intervention	High
Mills 2014[60]	14(14)	ACB	Digital	Adherence	Positive	Population, Intervention	High
Mizuno 2018[61]	20(5)	PWID	Diverse	Adherence, Retention	Positive, Positive	Design	Low
Muessig 2015[62]	23(21)	MSM, ACB, PWID	Digital	Initiation, Adherence, Retention	Indeterminate, Indeterminate	Evidence	High
Murray 2017[63]	23(2)	ACB	Diverse	Adherence, Retention	Indeterminate, Indeterminate	Population	Unclear
Musayon-Oblitas 2018[64]	9 (9)	None	Behavioral	Adherence	Positive	Evidence, Intervention	Low
Mutasa-Apollo 2017[65]	11(3)	ACB	Health system	Adherence, Retention	Neutral, Positive	Evidence	Low
Nachega 2016[66]	22(11)	MSM, PWID, CSW	Peer or community based	Adherence, Retention	Positive, Positive	Population, Design	Low
Parienti 2009[67]	11(11)	None	Medication modification	Adherence	Positive	None	High

Park 2014[68]	29(5)	MSM	Digital	Adherence	Positive	Intervention	Low
Perazzo 2017[69]	6(4)	MSM, PWID	Diverse	Adherence	Positive	Evidence	Unclear
Purnomo 2018[70]	16(7)	MSM, PWID, CSW	Digital	Initiation, Adherence, Retention	Positive, Positive, Positive	Design	Low
Quintana 2018[71]	26(19)	ACB	Digital	Adherence, Retention	Positive, Neutral	Population, Intervention	Low
Ramjan 2014[72]	21(6)	ACB	Medication modification	Adherence	Positive	Evidence	Low
Ridgeway 2018[73]	52(29)	ACB	Diverse	Adherence	Positive	Population	Low
Riley 2015[74]	11 (6)	MSM, ACB	Behavioral	Adherence	Positive	Evidence, Intervention, Comparison	High
Risher 2017[75]	152(14)	MSM, PWID	Diverse	Adherence, Retention	Positive, Positive	Evidence, Population, Intervention, Design	Low
Robbins 2014[76]	10(12)	MSM, ACB	Diverse	Adherence	Indeterminate	Population, Intervention, Design	Unclear
Rocha 2015[77]	4(4)	None	Pharmacy	Adherence	Neutral	Design	Low
Rueda 2006[78]	19(19)	MSM, ACB, PWID, Immigrants	Diverse	Adherence	Positive	Outcome, Design	Low
Ruzagira 2017[79]	14(3)	ACB	Peer or community based	Initiation	Neutral	Design	Low
Saberi 2011[80]	36(3)	None	Digital	Adherence	Positive	Intervention	Low
Saberi 2012[81]	32(2)	MSM, ACB	Pharmacy	Adherence	Positive	Intervention	Low
Scott-Sheldon 2017[82]	21(21)	ACB	Diverse	Adherence	Positive	Intervention	Low
Sharma 2016[83]	126(6)	MSM, ACB	Peer or community based	Initiation, Retention	Positive, Positive		Low
Shaw 2016[84]	10(3)	MSM, ACB	Diverse	Adherence	Positive	Population, Design	High
Suthar 2017[85]	4(1)	ACB	Economic	Adherence, Retention	Neutral, Positive	Evidence	Low

Swann 2018[86]	38(9)	ACB, PWID	Economic	Adherence, Retention	Positive, Positive	Evidence, Design	High
Tang 2015[87]	21(5)	ACB	Diverse	Retention	Indeterminate	Evidence, Intervention	High
van Camp 2013[88]	10(7)	ACB	Task shifting	Adherence	Positive	Design	Unclear
van der Heijden 2017[89]	16(19)	MSM, ACB	Behavioral	Adherence	Neutral	Evidence, Population	Low
van Velthoven 2012[90]	9(9)	PWID	Digital	Adherence	Neutral	Population	Low
van Velthoven 2013[91]	21(4)	ACB	Digital	Adherence	Neutral	Design	High
Vervloet 2012[92]	13(5)	None	Digital	Adherence	Positive	Population, Intervention	Low
Vojnov 2016[93]	30(3)	ACB	Health system	Initiation	Positive	Evidence	Low
Wise 2008[94]	21(8)	None	Digital	Adherence	Indeterminate	Evidence, Design	High
Wouters 2012[95]	29(7)	ACB	Peer or community based	Adherence	Positive	Design	Unclear
Wynberg 2014[96]	15(1)	ACB, Immigrants	Health system	Initiation, Retention	Neutral, Neutral	Intervention	Low
Yang 2014[97]	11(11)	None	Diverse	Adherence	Positive	Design	Unclear
Young 2010[98]	13(13)	ACB	Peer or community based	Adherence, Retention	Positive, Positive	Evidence, Population	Low

ACB: African, Caribbean and Black people; CSW: commercial sex workers; MSM: men who have sex with men; PWID: people who inject drugs; RCTs: randomized controlled trials; RoB: risk of bias.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	online supplementary appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	online supplementary appendix 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	online supplementary appendix 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8 (figure 3)
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10-11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

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BMJ Open

An overview of systematic reviews on strategies to improve treatment initiation, adherence to antiretroviral therapy and retention in care for people living with HIV: part 1

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An overview of systematic reviews on strategies to improve treatment initiation, adherence to antiretroviral therapy and retention in care for people living with HIV: part 1

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Key words:

HIV, antiretroviral therapy, adherence, retention, pragmatic

Word count:

Abstract

Objectives:

We sought to map the evidence, and identify interventions that increase initiation of antiretroviral therapy, adherence to antiretroviral therapy and retention in care for people living with HIV at high risk for poor engagement in care.

Methods:

We conducted an overview of systematic reviews and sought for evidence on vulnerable populations (men who have sex with men, African, Caribbean and Black people, sex workers, people who inject drugs and indigenous people). We searched PubMed, EMBASE, CINAHL, PsycINFO, Web of Science and the Cochrane Library in November 2018. We screened, extracted data and assessed methodological quality in duplicate and present a narrative synthesis.

Results:

We identified 2420 records of which only 98 systematic reviews were eligible. Overall, 65/98 (66.3%) were at low risk of bias. Systematic reviews focused on African, Caribbean and Black (66/98; 67.3%), men who have sex with men (32/98; 32.7%), people who inject drugs (6/98; 6.1%), sex workers and prisoners (both 4/98; 4.1%). Interventions were: mixed (37/98; 37.8%), digital (22/98; 22.4%), behavioral or educational (9/98; 9.2%), peer or community-based (8/98; 8.2%), health system (7/98; 7.1%), medication modification (6/98; 6.1%), economic (4/98; 4.1%), pharmacy based (3/98; 3.1%),or task-shifting (2/98; 2.0%). Most of the reviews concluded that the interventions worked (69/98; 70.4%), 17.3% (17/98) were neutral or were indeterminate12.2% (12/98). Knowledge gaps were the types of participants included in primary studies (vulnerable populations not included), poor research quality of primary studies and poorly tailored interventions (not designed for vulnerable populations). Digital, mixed and peer/community-based interventions were reported to be effective across the continuum of care.

Conclusions:

Interventions along the care cascade are mostly focused on adherence and do not sufficiently address all vulnerable populations.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To the best of our knowledge, this is the first overview to address the whole cascade of care for people living with HIV
- Our categorization of systematic reviews by intervention type and the intervention's success will permit decision makers to easily identify the interventions that are likely to work for their specific context
- We categorized systematic reviews to facilitate data synthesis, however we acknowledge that certain interventions may fit into multiple categories
- Among mixed interventions, it was challenging to determine the role of the individual intervention types on the overall effect
- This report at the systematic review level does not cover all aspects of the interventions, which can only be retrieved from individual trials

Background

Despite advances in diagnosis and management of HIV infection, many people living with HIV still do not have optimal outcomes. In 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDS) set the 90-90-90 target for 2020.[1] If this target is met, 90% of people living with HIV will know their HIV status; 90% of all people diagnosed with HIV will be receiving antiretroviral therapy (ART) and 90% of all people on ART will be virally suppressed.[1] These targets are contingent on engagement in the cascade of care that includes access to testing, timely diagnosis, access to and initiation of treatment, adherence to treatment and retention in care. Despite national efforts, very few countries have actually met these targets.[2] The UK has met these targets[3] and Botswana and Australia are on track.[4] Canada is also on track to meet these targets, with 87% of people with HIV diagnosed, 82% on treatment and 93% virally suppressed.[5] For countries to meet these targets, there must be policies in place to support programs that deliver interventions across the entire cascade of care. As such, there must be awareness, reductions in stigma and incentives that promote testing alongside strategies to enhance treatment initiation, adherence and retention in care. [6] Consistent access to ART and high-quality data should be collected so that advances towards the targets can be measured appropriately.[6]

If all these conditions are met and countries meet these targets, there are still concerns that the targets may be met at a national level but not in certain sub-populations. [7,8] The literature suggests that vulnerable populations such as men who have sex with men (MSM), sex workers (SW), people who inject drugs (PWID), people with precarious migration status and ethno-racial minorities have a higher disease burden, worse engagement in care and are less likely to achieve viral suppression.[9-14] MSM and SWs all over the worlds are 19 and 13.5 times more likely to be living with HIV.[7,8] In Canada, inequities in social and structural determinants such as injection drug use, ethno-racial background, age, housing, sex work and gender affect engagement in care.[11-15]

The literature is rife with interventions aimed at improving different aspects of the care cascade. However, the challenges countries face in achieving the UNAIDS targets suggests that the interventions may not be effective, may not be properly translated into practice, or may not be tailored (designed to have optimal impact on groups with different sociodemographic or risk characteristics that could influence the effect of the intervention) to the relevant populations. Therefore, due consideration of the settings in which interventions are tested, their target populations, complexity and applicability in the real world are important considerations for scale up.[16,17] These limitations in the quality and quantity of evidence were identified in the International Association of Physicians in AIDS Care (IAPAC) guideline document.[18]

While HIV is still a leading cause of disease burden in sub-Saharan Africa,[19] vulnerable populations in high income countries may experience a comparable disease burden if they are not recognised as a priority.[20] As countries strive to meet the 90-90-90 targets, it is becoming apparent that due to the disparities in outcomes across jurisdictions and populations, better targeted approaches are required to improve engagement in care.[21] Ontario is the most populous province of Canada and home to 42% of Canada's 71000 people living with HIV. Due to individual, social and structural factors, it is estimated that approximately 20% of these people living with HIV in Canada have discontinuous care.[11] In Ontario, 80-87% of people living with HIV are in care, 70-82% are on ART and 67-81% are virally suppressed.[22] This overview of systematic reviews will inform policy, practice and research in Ontario and other high-income settings especially with regards to engagement in HIV care for vulnerable populations. We sought to map the available evidence on strategies that improve engagement in the HIV care cascade (initiation of treatment, adherence to medication and retention in care) for priority populations as well as to identify knowledge gaps. See figure 1.

This overview is the first part of our report and includes a high-level summary of the findings from systematic reviews, with no distinction by country. We provide a map of the evidence here, and the second part will summarise the findings from the randomized trials included in the systematic reviews.

Figure 1: Outline of the HIV care cascade

Methods

We conducted an overview of systematic reviews using standard Cochrane methods.[23] The protocol for this overview has been published elsewhere.[24] Key features of our methods are outlined below.

Patient and public involvement:

Our research question was formulated and refined based on input from the Ontario HIV Treatment Network (OHTN), a non-profit network, as part of their strategy to close gaps in the cascade of care for key populations. The investigators include patients, clinicians, researchers and representatives of AIDS Service Organizations/Community-Based Organizations (ASO/CBOs). Decision makers and representatives from the Ministry of Health and Long-Term Care (MOHLTC) of Ontario were also consulted.

Criteria for considering reviews for inclusion

We included any systematic reviews with at least one study with a randomized comparison of an intervention designed to improve initiation of ART, adherence to ART and/or retention in care among people living with HIV. We excluded abstracts, non-systematic reviews and other overviews. All comparators (e.g. attention control, usual care, another intervention etc.) were eligible for inclusion. We had no restriction on the location of the studies or the ages of the participants.

Search methods for identification of reviews

We conducted an exhaustive and comprehensive search of the following databases: PubMed, EMBASE (Exerpta Medica Database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), PsycINFO, Web of Science and the Cochrane Library; from1995 (when combination ART was introduced) to 13 November 2018. The search strategy was reviewed by a Librarian at Health Sciences Centre Library at McMaster University. The full search strategy is reported as a supplementary file (online supplementary appendix 1).

We also searched the websites of the World Health Organization (WHO), United Nations Programme on HIV/AIDS (UNAIDS), National Institute for Health and Care Excellence (NICE) and the systematic review database housed at the Ontario HIV Treatment Network (OHTN): Synthesized HIV/AIDS Research Evidence (SHARE; http://www.hivevidence.ca/frmSearch.aspx).

Finally, we looked for additional systematic reviews in the bibliographies of the included reviews.

Screening

The results of our search were collated in EndNote reference manager.[25] Duplicates were removed and all the references were uploaded unto DistillerSR (Evidence Partners, Ottawa, Canada). We screened the retrieved citations in duplicate with reviewer pairs (BZ, AW, AH) first by examining the titles and abstracts and secondly by examining the full texts. Systematic reviews that met our inclusion criteria were processed and data were extracted.

Data items

From the systematic reviews, we extracted standard bibliometric data (author, year), number of included primary studies and their designs, target populations, types of interventions, outcomes of interest, key findings and knowledge gaps. Data were extracted in duplicate by reviewers working in pairs (BZ, AW, AH).

Assessment of methodological quality of included reviews

We appraised the methodological quality of the included reviews using the risk of bias in systematic reviews (ROBIS) tool.[26] This tool allows reviewers to assess the relevance of the question, identify concerns with the review process and make a judgement on risk of bias (high, low, unclear). Risk of bias was appraised in duplicate by pairs of reviewers (BZ, AW, AH).

Discrepancies and disagreements in screening, data extraction and risk of bias were resolved by consensus or by adjudication by a third reviewer (LM).

Data synthesis

The extracted data were described narratively. Systematic reviews were organised according to the portion of the care cascade they addressed (i.e. initiation, adherence, retention) and the intervention types: behavioral or educational, digital, mixed, economic, health system, medication modification, peer or community-based, pharmacy based or task-shifting. These categories were developed post-hoc to facilitate data synthesis. The types of interventions included in each category are outlined in Table 1.

Table 1: Categorization of intervention types in the systematic reviews

Intervention category	Types
Behavioral & Educational	Medication-assisted therapy, mindfulness-based stress reduction, motivational interviewing, psychotherapy, relaxation
Digital	Digital technology-based interventions such as alarms, electronic pillboxes, and pagers, mobile device text messages and voice messages, computer-based or internet-based interventions, online support communities and electronic medication packaging
Mixed	Combinations of any of the listed categories
Economic	Food assistance, cash incentives, performance-based financing, household economic strengthening
Health system	Point of care services, decentralised services, less frequent visits
Medication modification	Single tablet regimens, fixed dose combinations, rapid medication initiation, observed therapy
Peer or community-based	Home-base care, community-based services including the use of community health workers, lay health workers, treatment buddies, field officers, peer educators, volunteers and counsellors.
Pharmacy-based	Changes to standard pharmacy service delivery, pharmacist delivered interventions
Task-shifting	Service delivery by non-doctor staff, nurse-led interventions

Conclusion statements were categorized according to a previously used framework: positive (evidence of effectiveness); neutral (no evidence of effectiveness or no opinion); negative (authors advise against the use of intervention); indeterminate (insufficient evidence or more research is required).[27] Knowledge gaps were operationalised according to guidance on how to report research recommendations by identifying the state of the evidence, participants, interventions, comparisons and outcomes for which further research is needed.[28] We also discuss our findings within the scope of the Health Systems Arrangement Framework.

[29] In this framework, interventions may be organized to inform different parts of the decision-making process, and interventions can be related to governance, financial or delivery arrangements. [29] Interventions effects are summarised according to the vulnerable population they were tested with, intervention target (initiation, adherence, retention) and risk of bias. Interventions reported in systematic with positive recommendations are highlighted. Our findings are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [30]

Results

Literature search:

Our search identified 2,420 records from electronic databases and 76 from other sources. After removal of duplicates, 1505 titles and abstracts were screened, of which 1006 were considered ineligible and excluded. We further screened 499 full text articles and included 98. Agreement on the screening of full text articles was high (Kappa=0.79). The screening process is outlined in a PRISMA flow diagram (Figure 2).[30] A full list of excluded systematic reviews is provided as a supplementary file (online supplementary appendix 2)..

Figure 2: Systematic review flow diagram

Description of included reviews

The 98 included systematic reviews were published between 2006 and 2018[31-128] and reported on interventions to improve initiation of care (n=18),[32,41,54,58,61,64,65,70,75,78,81,84,92,100,109,113,123,126] adherence to ART (n=82)[31-36,38,39,41-53,55,57,59,60,62,65-68,71-77,79-108,110-112,114-116,118-122,124,125,127,128] and retention in care (n=39).[32,37,40,41,52,56,58-60,63-66,68-70,75-78,81,84,86,88,89,91-93,95,96,100,101,105,113,115-117,126,128] Thirty-one (31) reviews reported two or more aspects of the cascade.[32,41,52,58-60,64-66,70,75-78,81,84,86,88,89,91,92,95,96,100,101,105,113,115,116,126,128] They included a median (quartile 1; quartile 3 [Q1; Q3]) of 19 (11;28) primary studies and 8(4;13) randomized trials.

With regards to vulnerable populations, 32.7% (32/98) included primary studies involving MSM,[31,33,40-42,45,47,48,51,52,59,65,70,73,80,81,85,87,89,92,96,98-100,104-106,108,110,113,114,119] 67.3% (66/96) involving African, Caribbean or Black People,[31-34,36,37,40,43,45,47,48,50,52-54,56,58-61,63-66,70,71,73-82,84-87,89,90,92,93,95,101-104,106,108-110,112-120,123,125,126,128] 25.5% (25/98) focused on PWID,[39,41,43,44,48,50-52,60,66,68,70,73,74,85,88,91,92,96,99,100,105,108,116,121] 6.1% (6/98) involving SW,[41,42,48,52,96,100] 4.1% (4/98) included data on immigrants, [42,82,108,126] and 4.1% (4/98) included data on incarcerated persons.[40,60,91,105] These characteristics are summarised in table 2. A full list of the 98 included systematic reviews is reported as a supplemental file (online supplementary appendix 3).

Table 2: Summary characteristics of included systematic reviews: n=98

Variable	Statistic
Year: median (quartile 1; quartile 3)	2015 (2013;2017)
Number of included primary studies: median (quartile 1; quartile 3)	29 (11; 28)
Number of randomized trials: median (quartile 1; quartile 3)	8 (4;13)
Vulnerable populations included: n (%)	
African, Caribbean or Black	66 (67.3)
Men who have sex with men	32 (32.7)

People who inject drugs	25 (25.5)
Sex workers	6 (6.1)
Immigrants	4 (4.1)
Incarcerated persons	4 (4.1)
Intervention categories: n (%)	
Mixed	37 (37.8)
Digital	22 (22.4)
Behavioral or educational	9 (9.2)
Peer or community based	8 (8.2)
Health system	7 (7.1)
Medication modification	6 (6.1)
Economic	4 (4.1)
Pharmacy	3 (3.1)
Task shifting	2 (2.0)
Care cascade outcomes: n (%) *	
Adherence	82 (59.0)
Retention	39 (28.1)
Initiation	18 (12.9)

*not mutually exclusive

Methodological quality of included reviews

Most of the systematic reviews were judged to be a low risk of bias (65 [66.3%]). Twenty (20.4%) were judged to be at high risk of bias and 13 (13.3%) were judged to be at unclear risk of bias. The most frequent concern was related to data collection and primary study appraisal (28.6% at high risk of bias in this domain). The main concerns we identified were no risk of bias assessments conducted, missing primary study information and no evidence that data had been processed in duplicate. This was followed by the risk of bias in the identification and selection of primary studies (19.4% at high risk of bias in this domain). The main limitations we identified were not searching grey literature, searching less than 2 databases, exclusion of non-English primary studies, no evidence that data were processed in duplicate and not reporting the search strategy. For the domain of study eligibility criteria (15.3% at high risk of bias in this domain) the main concerns were: eligibility criteria not described in sufficient detail, ambiguous criteria and restrictions based on publication status and language. For the domain of synthesis and findings (15.3% at high risk of bias in this domain) the main concerns were: heterogeneity was not assessed, choice of synthesis approach not justified and primary study biases not addressed. See figure 3 and online supplementary appendix 3.

Figure 3: Risk of bias summary

Effects of interventions

Most systematic reviews gave positive recommendations for the interventions they examined (69/70.4%). Seventeen (17.3%) were neutral and 12 (12.2%) were indeterminate. No systematic reviews recommended against any interventions. Positive findings from systematic reviews are outlined below. All our findings, positive, negative, neutral and indeterminate are summarised in a supplementary file (online supplementary appendix 3).

Initiation

Of the 18 systematic reviews that examined initiation of ART as an outcome, 11 (61.1%) at low risk of bias reported that digital,[41,100] mixed,[32,54,75,84] health system [66,78,123] and peer or community-based

interventions [65,113] improved initiation of ART. Two systematic reviews at high or unclear risk of bias reported that digital,[64] and mixed interventions improved initiation of ART.[70]

Adherence

Of the 82 systematic reviews that examined adherence to ART as an outcome, 25 (30.5%) at low risk of bias reported that behavioral/educational,[44,45] digital,[31,33,41,46,52,79,98,100,101,111,122] mixed,[32,36,43,53,57,62,72,74,75,82,84,91,103,105,108,112] health system,[50] medication modification,[49,59,102] peer/community-based,[73,96,128] pharmacy[86,111] and task-shifting interventions[77] improved adherence to ART. Eighteen (18/21.9%) systematic reviews at high or unclear risk of bias reported that behavioral/educational,[39,104] digital,[42,71,85,90] mixed,[50,80,89,99,114,127] economic,[55,68,116] medication modification,[97] peer or community-based[125] and task-shifting [118]interventions improved adherence to ART.

Retention

Of the 39 systematic reviews that examined retention in care as an outcome, 21 (53.8%) systematic reviews at low risk of bias reported that digital,[41,52,100] mixed,[32,66,69,75,84,91,105] economic,[115] health system,[66,78,95] medication modification,[59] peer/community-based[65,96,113,128] and task shifting[77] interventions improved adherence to HIV care. Seven (7/17.9%) of systematic reviews at high or unclear risk of bias reported that behavioral/educational,[37] digital,[64] mixed,[70,89] economics,[116] health system[40] and peer or community-based interventions[56] improved retention in care.

Figure 4 is a display of the available evidence, showing intervention type by HIV care cascade target (panel a), intervention type by authors' conclusions (panel b) and key population by HIV care cascade target (panel c).

Knowledge gaps

The most frequent knowledge gap identified in 22 (22.4%) systematic reviews was with regards to the population studied, where further investigation with vulnerable and marginalized groups such as children, youth, MSM, pregnant and breast-feeding women, individuals in low-income settings, individuals with concurrent mental health issues and older adults is required. The authors also raised concerns about the primary study designs (n=22/22.4%), and primarily called for more robust, innovative, rigorous and high-quality designs, including experimental designs, (pragmatic) randomized trials, longer follow-up times, mixed methods approaches, and primary studies with larger sample sizes. The nature of the intervention was also identified as a knowledge gap (22/22.4%). The authors found that interventions were not sufficiently tailored to high-risk populations, low-income settings, were too costly or didn't cover the entire cascade of care. They further suggested that novel interventions be investigated, and older intervention be combined to assess synergistic effects. Only two (2.0%) systematic reviews raised concerns about the nature of the outcomes used.[72,83] They called for universal definitions for adherence and the use of more humanistic, economic and patient-important outcomes.

Discussion

We conducted an exhaustive and comprehensive search for systematic reviews focused on examining interventions that enhance ART initiation, ART adherence and retention among people living with HIV. We included 98 systematic reviews. Most of the systematic reviews we identified focused on adherence enhancing interventions and investigated a mixed range of intervention categories. For the most part, the authors of the included systematic reviews found that the interventions were effective (70.4%). Digital, mixed and peer/community interventions were the only three categories of interventions that were reported to be effective across the whole continuum of care. The main knowledge gaps identified in most systematic

reviews was a lack of focus on the populations that would benefit the most (22.4%), poor quality of the primary studies (22.4%) and nature of the interventions. (22.4%).

We further examined to what extent health systems arrangements were met by this body of evidence. Most systematic reviews focused on the delivery of interventions (task-shifting, homebased care, pharmacy-based interventions etc.) but none addressed governance of HIV care and very few addressed financial components (food assistance, cash incentives, performance-based financing, household economic strengthening) that may support or hinder access to HIV care and treatment. [55,68,115,116] This may be an important limitation in how research is designed, without adequate consideration of the facets of a health system that could influence outcomes.

Most of the systematic reviews were at low risk of bias (66.3%).[26] However, there were some concerns, notably with issues related to reporting of details in review conduct which indicated high or unclear risk of bias. We recognise that journal word count limitations may prevent authors from reporting all the relevant details, but appendices could be used to provide additional details. Risk of bias from these systematic reviews should be interpreted in context and may differ from the risk of bias in the primary studies included.

To the best of our knowledge, there is no other overview of systematic reviews investigating the cascade of HIV care, but our findings confirm previous research indicating a paucity of research on vulnerable populations,[129] and challenges with scaling-up interventions.[130]

The disproportionate study of adherence might be due to it's perceived importance as a cornerstone of care, or the relative ease of designing adherence studies. Prior to recent recommendations to treat all diagnosed people, initiation of treatment was seldom a priority. [131]Likewise, retention in care is an outcome that requires substantially longer follow up to generate meaningful results.[11,132] In order for countries to meet the 90-90-90 target, the cascade of care must be viewed as continuum, not just for practice, but also for research, such that interventions that strengthen the entire cascade be scaled up.

Even though only disparate definitions of adherence to ART were identified by the authors of some systematic reviews, we believe such diversity may exist with retention in care, as other studies have noted that there is no gold standard for what constitutes adequate retention. [133] Future work on the trials included in the systematic reviews will permit us the describe the breadth of definitions used for both adherence and retention. Standardized definitions are important for jurisdictions to be able to measure changes over time and make cross jurisdictional comparisons. Standardized definitions will also help systematic reviewers to synthesize research.

Strengths and limitations:

We acknowledge the following limitations. Despite our attempt to group the interventions into categories, we recognise that certain interventions may fit into more than one category. For example, tasking shifting and pharmacy-based interventions can be viewed as health system or community based interventions. Secondly, for the group of systematic reviews that investigated mixed interventions, it is challenging to determine the role of the individual intervention types on the overall effect. This group could contain interventions from any category and therefore it is not surprising that the systematic reviews that included mixed interventions often found a significant effect. Within each systematic review, the diversity of study designs, populations and primary studies from various income levels precluded in-depth investigation of how these issues may have affected intervention effectiveness at the systematic review level. No distinction was made between ACB populations in their respective countries versus ACB populations in high income countries where the vulnerability is different. Further ongoing work on the trials included in these systematic reviews will highlight the features of interventions in ACB populations. Some primary studies are included in more than one systematic review. This highlights the need for a primary study-level analysis. Also, we

reiterate that the statements on effectiveness are drawn from the concluding statements from the included systematic reviews and should therefore be interpreted with caution. Finally, despite our efforts to conduct a comprehensive and exhaustive search, it is possible that some systematic reviews were missed if they were indexed with terms we did not include in our strategy.

This work has many strengths. In addition to using a predefined protocol, we conducted a comprehensive search, assessed risk of bias, investigated the availability of data on vulnerable populations and categorised the systematic reviews by type of intervention and success of the intervention. This approach would permit decision makers and other end users to identify intervention type that are likely to work for specific populations at each point of the care cascade. However, a trial-level analyses is required to enrichen these findings.

Conclusion:

We found limited research on vulnerable populations and uneven focus on the three aspects of the care cascade. In order to identify the most effective and pragmatic interventions for vulnerable populations in high income settings, a study-level analysis is required. The diversity of the interventions examined and the populations studied indicate the need for network meta-analyses in this field, some of which have already been published.[90] The lack of systematic reviews that generate evidence on governance is indicative of how removed many research endeavours are from policy-making. Monitoring and evaluation also need to be considered within systems to support up-to-date collection of data on detection, initiation, adherence and retention in care.

Differences between protocol and review

There are a few differences between this report and the protocol. First, after additional consultation with stakeholders we included interventions targeting initiation of ART. Given the amount of data, we decided to report our findings on two levels, the systematic review level and the primary study level. Only the systematic review level is reported here, and therefore in-depth analyses of the settings (high versus low income) of the primary studies and the levels of pragmatism, and certainty of the evidence are reserved for a second paper.

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Authors contributions

LM developed the first draft of the manuscript. AH, AW, LM, BZ extracted data and created tables. EA, DOL, BR, MS, DM, LPR, CL, SM, AB, WH, AH, AW, BZ and LT revised several versions of the manuscript and approved the final version. LM is the guarantor of the manuscript.

Declarations of interest

The authors declare none.

Data availability

All data relevant to the study are included in the article or uploaded as supplementary information

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Figure legends:

Figure 1: Outline of the HIV care cascade

Figure 2: Systematic review flow diagram

Figure 3: Risk of bias summary

Figure 4: Evidence maps of HIV care cascade interventions

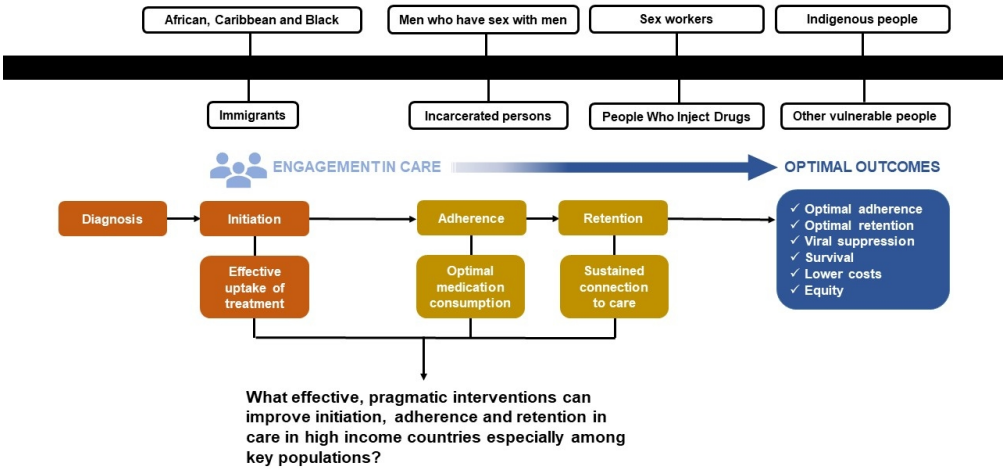

Figure 1: Outline of the HIV care cascade

108x60mm (300 x 300 DPI)

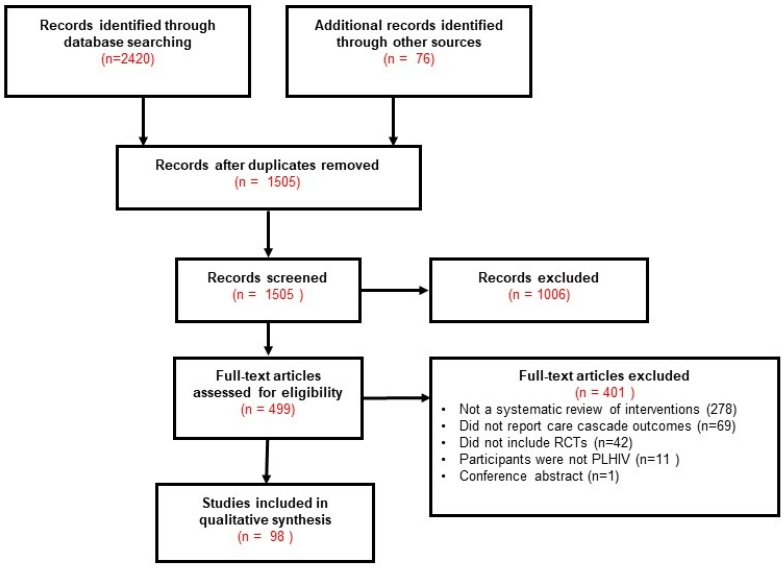

Figure 2: Systematic review flow diagram

81x60mm (300 x 300 DPI)

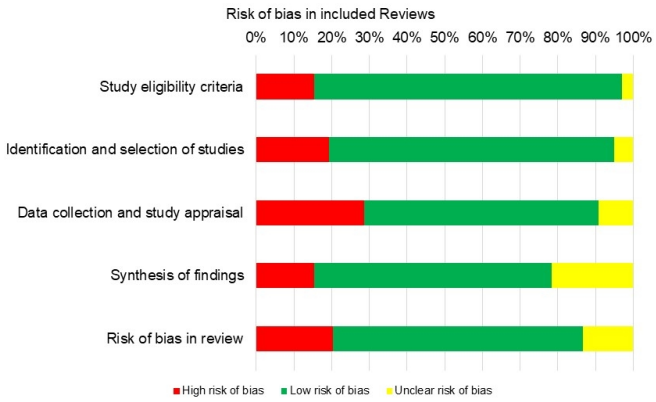

Figure 3: Risk of bias summary

108x60mm (300 x 300 DPI)

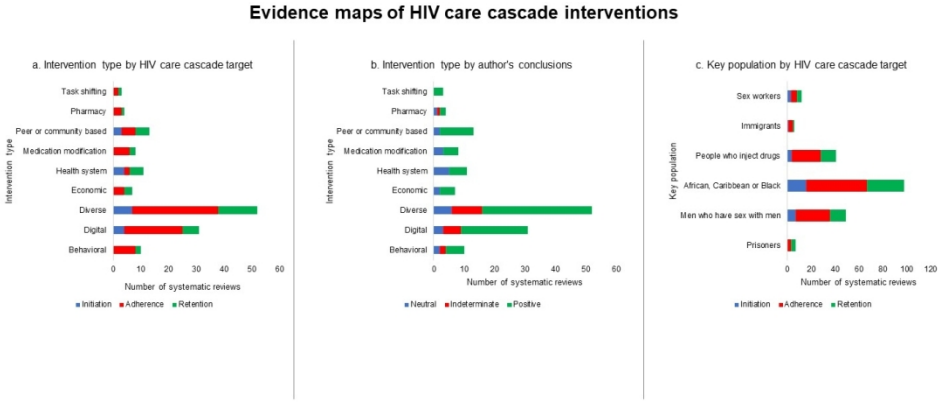

Figure 4: Evidence maps of HIV care cascade interventions

400x190mm (96 x 96 DPI)

Supplement 1: Search strategy

November 12 & 13, 2018: N = 2420

DATABASES:
CINAHL, N = 195 (Nov-13)
Cochrane Library of Systematic Reviews, N = 217 (Nov-13)
Embase, N = 947 (Nov-12)
PsycINFO, N = 105 (Nov-12)
PubMed, N = 304 (Nov-13)
Web of Science, N = 652 (Nov-13)

SEARCH METHODS (as per protocol manuscript):

- From 1995 to present (when combination ART was introduced), no language restrictions: Systematic review OR meta-analysis
+ Adhere*nce OR complian*ce OR retention OR dropouts OR los*s adj2 to follow-up OR attrition OR nonadheren* OR uncompliant* OR treatment refusal OR persistence OR non-persistence OR initiat* OR start* OR uptake
+ HIV OR human immune-deficiency virus OR human immuno-deficiency virus
+ Antiretroviral therapy OR antiretrovirals OR antiretroviral treatment OR Highly Active Antiretroviral Therapy OR ART or HAART

Librarian Consult (November 12, 2018)
Q: Verify adequate capture of HIV SRs

- impossible to get MeSH for all keywords but make sure to get good subject headings for the main concepts at the very least (e.g. antiretroviral treatment, HIV)
- fix truncated terms 'adherence', 'uncompliant*'
- could add adj2 for los* to follow-up
- good practice to use explode throughout

Q: Verify CINAHL searching

- doesn't use MeSH, need to look up subject headings (uncheck box to get the key word)
- re: WoS – use 'SU' to ~ represent search in all fields

Database: CINAHL via EBSCOhost Research Databases
Completed on: November 13, 2018
Search Strategy:

S1	(MH "Systematic Review")	68,246
S2	(MH "Meta Analysis")	35,345
S3	S1 OR S2	87,072
S4	(MH "Patient Compliance+") OR (MH "Treatment Refusal") OR (MH "Medication Compliance")	46,042
S5	(MH "Research Subject Retention")	692
S6	(MH "Research Dropouts") OR (MH "Patient Dropouts")	2,506
S7	(MH "After Care")	11,133
S8	adhere* OR nonadhere* OR complian* OR uncomplian* OR retention OR dropout OR lost to follow-up OR attrition OR treatment refusal OR persistence OR non-persistence OR initiat* OR start* OR uptake	339,844
S9	S4 OR S5 OR S6 OR S7 OR S8	349,538
S10	(MH "Human Immunodeficiency Virus+")	8,168
S11	(MH "HIV-Infected Patients+") OR (MH "HIV Infections+")	80,662
S12	HIV OR human immun* deficiency virus	96,874
S13	S10 OR S11 OR S12	104,864
S14	(MH "Antiretroviral Therapy, Highly Active")	5,519
S16	antiretroviral therapy OR antiretrovirals OR antiretroviral treatment OR anti-HIV agents OR anti-retroviral agents OR Highly Active Antiretroviral Therapy OR HAART	24,400
S17	S14 OR S15 OR S16	26,013
S18	S3 AND S9 AND S13 AND S17	**195**

(Limiter: Published Date: 19950101-20181231)
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Database: Cochrane Database of Systematic Reviews
Completed on: November 13, 2018 (updated search from 216 results on Nov-7)
Search Strategy:

'systematic review OR meta-analysis in All Text AND adherence OR compliance OR retention OR dropouts OR loss to follow-up OR attrition OR nonadheren* OR uncompliant* OR treatment refusal OR persistence OR non-persistence OR initiat* OR start* OR uptake in All Text AND HIV OR human immune-deficiency virus OR human immuno-deficiency virus in All Text AND antiretroviral therapy OR antiretrovirals OR antiretroviral treatment OR Highly Active Antiretroviral Therapy OR ART or HAART in All Text - with Cochrane Library publication date Between Jan 1995 and Dec 2018 (Word variations have been searched)' (216)

'adhere* OR nonadhere* OR complian* OR uncomplian* OR retention OR dropout OR lost to follow-up OR attrition OR treatment refusal OR persistence OR non-persistence OR initiat* OR start* OR uptake in All Text AND HIV OR human immun* adj2 deficiency virus in All Text AND antiretroviral therapy OR antiretrovirals OR antiretroviral treatment OR anti-HIV agents OR anti-retroviral agents OR Highly Active Antiretroviral Therapy OR ART OR HAART in All Text - with Cochrane Library publication date Between Jan 1995 and Dec 2018 (Word variations have been searched)' **(217)**
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Database: Embase <1974 to 2018 November 09> via Ovid
Completed on: November 12, 2018 (updated search from 720 results on Nov-7)
Search Strategy:

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1 systematic review.mp. or exp "systematic review"/ (241913)
2 meta analysis.mp. or exp "meta analysis"/ (232198)
3 (complian* or uncomplian*).mp. or exp "medication compliance"/ (306191)
4 retention.mp. (225178)
5 dropout.mp. or exp "patient dropout"/ (10447)
6 (los* adj2 to follow up).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (35898)
7 attrition.mp. (14277)
8 (adhere* or nonadhere*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (255209)
9 treatment refus*.mp. or exp "treatment refusal"/ (17490)
10 persistence.mp. (102883)
11 initiat*.mp. (789288)
12 start*.mp. (634133)
13 uptake.mp. (461506)
14 1 or 2 (366337)
15 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (2578956)
16 (HIV or human immune-deficiency virus or human immuno-deficiency virus).mp. (367212)
17 exp "human immunodeficiency virus"/ or exp "human immunodeficiency virus infection"/ or exp "human immunodeficiency virus infected patient"/ (452990)
18 16 or 17 (501218)
19 antiretroviral therapy.mp. or exp "antiretroviral therapy"/ (69407)
20 antiretrovirals.mp. (4928)
21 antiretroviral treatment.mp. (9740)
22 exp "antiretrovirus agent"/ (178047)
23 highly active antiretroviral therapy.mp. or exp "highly active antiretroviral therapy"/ (38980)
24 (ART or HAART).mp. (170581)
25 19 or 20 or 21 or 22 or 23 or 24 (340645)
26 14 and 15 and 18 and 25 (948)
27 limit 26 to yr="1995 -Current" **(947)**

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Database: PsycINFO <1987 to November Week 1 2018> via Ovid
Completed on: November 12, 2018 (updated search from 101 results on Nov-7)
Search Strategy:

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1 systematic review.mp. (21950)
2 meta analysis.mp. or exp "meta analysis"/ (25527)
3 1 or 2 (41919)
4 exp "compliance"/ or exp "treatment compliance"/ (16310)
5 (complian* or uncomplian*).mp. (32297)
6 dropout.mp. or exp "treatment dropout"/ (7191)
7 retention.mp. (34515)
8 attrition.mp. or exp "experimental attrition"/ (6818)
9 (los* adj2 to follow up).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (1103)
10 adhere*.mp. (31235)
11 treatment refus*.mp. or exp "treatment refusal"/ (886)
12 persistence.mp. (16819)
13 initiate.mp. (9915)
14 start*.mp. (82553)
15 uptake.mp. (13475)
16 nonadherence.mp. (1750)
17 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (215604)
18 HIV.mp. or exp "HIV"/ (52967)
19 (human immunodeficiency virus or human immune-deficiency virus or human immuno-deficiency virus).mp. (6071)
20 18 or 19 (53288)
21 exp "drug therapy"/ (121212)
22 (antiretroviral or antiretroviral therapy or antiretroviral treatment or ART or HAART).mp. (40678)
23 21 or 22 (158296)
24 3 and 17 and 20 and 23 (105)
25 limit 24 to yr="1995 -Current" **(105)**

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Database: PubMed <1995/01/01 to 31-Dec-2018>
Completed on: November 13, 2018 (updated search from 282 results on Nov-7)
Search Strategy:

((((((systematic review OR meta-analysis)) AND (adherence OR compliance OR retention OR dropouts OR loss to follow-up OR attrition OR nonadheren* OR uncompliant* OR treatment refusal OR persistence OR non-persistence OR initiat* OR start* OR uptake)) AND (HIV OR human immune-deficiency virus OR human immuno-deficiency virus)) AND (antiretroviral therapy OR antiretrovirals OR antiretroviral treatment OR Highly Active Antiretroviral Therapy OR ART or HAART)) AND systematic[sb]) AND systematic review[ti] (282)

((((((systematic review OR meta-analysis)) AND (adhere* OR nonadhere* OR complian* OR uncomplian* OR retention OR dropout OR lost to follow-up OR attrition OR treatment refusal OR persistence OR non-persistence OR initiat* OR start* OR uptake)) AND (HIV OR human immune-deficiency virus OR human immuno-deficiency virus)) AND (antiretroviral therapy OR antiretrovirals OR antiretroviral treatment OR Highly Active Antiretroviral Therapy OR ART OR HAART OR anti-HIV agents OR anti-retroviral agents)) AND systematic[sb]) AND systematic review[ti] Filters: Publication date from 1995/01/01 to 2018/12/31
(304)

MeSH headings [mh], captured via 'All Fields' search:
meta-analysis [publication type], meta-analysis as topic / review, systematic
patient dropouts / patient compliance (patient adherence/nonadherence) / treatment adherence and compliance (therapeutic adherence/compliance) / medication adherence (nonadherence, compliance/noncompliance) /lost to follow-up
HIV / anti-HIV agents / anti-retroviral agents / antiretroviral therapy, highly active (HAART)

systematic review	"review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "systematic review"[All Fields]
meta-analysis	"meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields]
retention	"retention (psychology)"[MeSH Terms] OR ("retention"[All Fields] AND "(psychology)"[All Fields]) OR "retention (psychology)"[All Fields] OR "retention"[All Fields]
lost to follow-up	"lost to follow-up"[MeSH Terms] OR ("lost"[All Fields] AND "follow-up"[All Fields]) OR "lost to follow-up"[All Fields] OR ("lost"[All Fields] AND "follow"[All Fields] AND "up"[All Fields]) OR "lost to follow up"[All Fields]
attrition	"tooth attrition"[MeSH Terms] OR ("tooth"[All Fields] AND "attrition"[All Fields]) OR "tooth attrition"[All Fields] OR "attrition"[All Fields]
treatment refusal	"treatment refusal"[MeSH Terms] OR ("treatment"[All Fields] AND "refusal"[All Fields]) OR "treatment refusal"[All Fields]
HIV	"hiv"[MeSH Terms] OR "hiv"[All Fields]
human	"humans"[MeSH Terms] OR "humans"[All Fields] OR "human"[All Fields]
immune-deficiency	"immunologic deficiency syndromes"[MeSH Terms] OR ("immunologic"[All Fields] AND "deficiency"[All Fields] AND "syndromes"[All Fields]) OR "immunologic deficiency syndromes"[All Fields] OR ("immune"[All Fields] AND "deficiency"[All Fields]) OR "immune deficiency"[All Fields]
virus	"viruses"[MeSH Terms] OR "viruses"[All Fields] OR "virus"[All Fields]
immuno-deficiency	"immunologic deficiency syndromes"[MeSH Terms] OR ("immunologic"[All Fields] AND "deficiency"[All Fields] AND "syndromes"[All Fields]) OR "immunologic deficiency syndromes"[All Fields] OR ("immuno"[All Fields] AND "deficiency"[All Fields]) OR "immuno deficiency"[All Fields]

therapy	"therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]
treatment	"therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]
Highly Active Antiretroviral Therapy	"antiretroviral therapy, highly active"[MeSH Terms] OR ("antiretroviral"[All Fields] AND "therapy"[All Fields] AND "highly"[All Fields] AND "active"[All Fields]) OR "highly active antiretroviral therapy"[All Fields] OR ("highly"[All Fields] AND "active"[All Fields] AND "antiretroviral"[All Fields] AND "therapy"[All Fields])
ART	"art"[MeSH Terms] OR "art"[All Fields]
HAART	"antiretroviral therapy, highly active"[MeSH Terms] OR ("antiretroviral"[All Fields] AND "therapy"[All Fields] AND "highly"[All Fields] AND "active"[All Fields]) OR "highly active antiretroviral therapy"[All Fields] OR "haart"[All Fields]
anti-HIV agents	"anti-hiv agents"[Pharmacological Action] OR "anti-hiv agents"[MeSH Terms] OR ("anti-hiv"[All Fields] AND "agents"[All Fields]) OR "anti-hiv agents"[All Fields] OR ("anti"[All Fields] AND "hiv"[All Fields] AND "agents"[All Fields]) OR "anti hiv agents"[All Fields]
anti-retroviral agents	"anti-retroviral agents"[Pharmacological Action] OR "anti-retroviral agents"[MeSH Terms] OR ("anti-retroviral"[All Fields] AND "agents"[All Fields]) OR "anti-retroviral agents"[All Fields] OR ("anti"[All Fields] AND "retroviral"[All Fields] AND "agents"[All Fields]) OR "anti retroviral agents"[All Fields]

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Database: Web of Science
Completed on: November 13, 2018
Search Strategy:

#1	TS=(systematic review OR meta-analysis)	271,168
#2	TS=(adhere* OR nonadhere* OR complian* OR uncomplian* OR retention OR dropout OR los* follow-up OR attrition OR treatment refusal OR persistence OR non-persistence OR initiat* OR start* OR uptake)	2,512,891
#3	TS=(HIV OR human immun* deficiency virus)	306,952
#4	TS=(antiretroviral therapy OR antiretrovirals OR antiretroviral treatment OR anti-HIV agents OR anti-retroviral agents OR ART OR Highly Active Antiretroviral Therapy OR HAART)	461,846
#5	#4 AND #3 AND #2 AND #1	**652**

(Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1995-2018)
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Supplement 2: List of excluded studies

Not a systematic review:

1. Abdulrahman, S. A.,Rampal, L.,Othman, N.,Ibrahim, F.,Kadir Shahar, H.,Radhakrishnan, A. P.. Socioeconomic Predictors of Adherence Behavior Among HIV-Positive Patients Receiving Antiretroviral Therapy in Selangor, Malaysia. Asia Pac J Public Health. 2017. 29:304-314
2. Abuogi, L. L.,Smith, C.,McFarland, E. J.. Retention of HIV-Infected Children in the First 12 Months of Anti-Retroviral Therapy and Predictors of Attrition in Resource Limited Settings: A Systematic Review. Plos One. 2016. 11:#pages#
3. Aderomilehin, O.,Hanciles-Amu, A.,Ozoya, O. O.. Perspectives and Practice of HIV Disclosure to Children and Adolescents by Health-Care Providers and Caregivers in sub-Saharan Africa: A Systematic Review. Front Public Health. 2016. 4:166
4. Aidala, A. A.,Wilson, M. G.,Shubert, V.,Gogolishvili, D.,Globerman, J.,Rueda, S.,Bozack, A. K.,Caban, M.,Rourke, S. B.. Housing Status, Medical Care, and Health Outcomes Among People Living With HIV/AIDS: A Systematic Review. Am J Public Health. 2016. 106:e1-e23
5. Alcorn, James Samuel. Evaluating the appropriateness of dosing adjustments in the coadministration of maraviroc and CYP3A inhibitors: A literature review. HIV & AIDS Review. 2016. 15:122-126
6. Aldir, I.,Horta, A.,Serrado, M.. Single-tablet regimens in HIV: does it really make a difference?. Curr Med Res Opin. 2014. 30:89-97
7. Anglemyer, A.,Rutherford, G. W.,Horvath, T.,Baggaley, R. C.,Egger, M.,Siegfried, N.. Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples. Cochrane Database Syst Rev. 2013. 2013 (4) (no pagination):CD009153
8. Anonymous,. Meeting Abstracts - Academy of Managed Care Pharmacy Nexus 2018. Journal of Managed Care and Specialty Pharmacy. Conference: Academy of Managed Care Pharmacy Nexus, AMCP. 2018. 24:#pages#
9. Arevalo, Maria Teresa Varela,Torres, Isabel Cristina Salazar,Sanchez, Diego Correa. Adherencia al tratamiento en la infeccion por HIV/AIDS. Consideraciones teoricas y metodologicas para su abordaje. Adherencia al tratamiento en la infeccion por VIH/SIDA. Consideraciones teoricas y metodologicas para su abordaje.. 2008. 11:101-113
10. Assawasuwannakit, P.,Braund, R.,Duffull, S. B.. A model-based meta-analysis of the influence of factors that impact adherence to medications. J Clin Pharm Ther. 2015. 40:24-31
11. Astuti, N.,Maggiolo, F.. Single-Tablet Regimens in HIV Therapy. Infect Dis Ther. 2014. 3:1-17
12. Barbara, Castelnuovo,Reynolds, Steven J.. Optimizing Treatment Monitoring in Resource Limited Settings in the Era of Routine Viral Load Monitoring. Current Tropical Medicine Reports. 2017. 4:1-5
13. Baril, J. G.,Angel, J. B.,Gill, M. J.,Gathe, J.,Cahn, P.,van Wyk, J.,Walmsley, S.. Dual Therapy Treatment Strategies for the Management of Patients Infected with HIV: A Systematic Review of Current Evidence in ARV-Naive or ARV-Experienced, Virologically Suppressed Patients. PLoS One. 2016. 11:e0148231
14. Barlow-Mosha, L.,Musiime, V.,Davies, M. A.,Prendergast, A. J.,Musoke, P.,Siberry, G.,Penazzato, M.. Universal antiretroviral therapy for HIV-infected children: a review of the benefits and risks to consider during implementation. J Int AIDS Soc. 2017. 20:21552

15. Barnighausen, T.. The role of the health system in HIV treatment-as-prevention. AIDS. 2010. 24:2741-2
16. Barroso, J.,Leblanc, N. M.,Flores, D.. It's Not Just the Pills: A Qualitative Meta-Synthesis of HIV Antiretroviral Adherence Research. J Assoc Nurses AIDS Care. 2017. 28:462-478
17. Beckham, S. W.,Beyrer, C.,Luckow, P.,Doherty, M.,Negussie, E. K.,Baral, S. D.. Marked sex differences in all-cause mortality on antiretroviral therapy in low- and middle-income countries: a systematic review and meta-analysis. J Int AIDS Soc. 2016. 19:21106
18. Berg, C. J.,Michelson, S. E.,Safren, S. A.. Behavioral aspects of HIV care: adherence, depression, substance use, and HIV-transmission behaviors. Infect Dis Clin North Am. 2007. 21:181-200, x
19. Berhan, A.,Berhan, Y.. Virologic response to tipranavir-ritonavir or darunavir-ritonavir based regimens in antiretroviral therapy experienced HIV-1 patients: a meta-analysis and meta-regression of randomized controlled clinical trials. PLoS One. 2013. 8:e60814
20. Bernaud, Camille,Rodallec, Audrey,Morrier, Marine,Allavena, Clotilde,Perre, Philippe,Pineau, Solene,Jovelin, Thomas,Hall, Nolwenn,Pineau, Samuel,Andre-Garnier, Elisabeth,Raffi, Francois. P017: Low virologic failure on TDF/FTC/RPV in HIV-infected naïve and virologically suppressed patients with strict clinical selection and/or DNA genotyping. Journal of the International AIDS Society. 2015. 18:17-18
21. Bezabhe, W. M.,Chalmers, L.,Bereznicki, L. R.,Peterson, G. M.. Adherence to Antiretroviral Therapy and Virologic Failure: A Meta-Analysis. Medicine (Baltimore). 2016. 95:e3361
22. Bock, P.,James, A.,Nikuze, A.,Peton, N.,Sabapathy, K.,Mills, E.,Fidler, S.,Ford, N.. Baseline CD4 Count and Adherence to Antiretroviral Therapy: A Systematic Review and Meta-Analysis. J Acquir Immune Defic Syndr. 2016. 73:514-521
23. Bolsewicz, K.,Debattista, J.,Vallely, A.,Whittaker, A.,Fitzgerald, L.. Factors associated with antiretroviral treatment uptake and adherence: a review. Perspectives from Australia, Canada, and the United Kingdom. AIDS Care. 2015. 27:1429-38
24. Braithwaite, R. S.,Shechter, S.,Roberts, M. S.,Schaefer, A.,Bangsberg, D. R.,Harrigan, P. R.,Justice, A. C.. Explaining variability in the relationship between antiretroviral adherence and HIV mutation accumulation. J Antimicrob Chemother. 2006. 58:1036-43
25. Brickley, Deborah,Butler, Lisa M.,Kennedy, Gail E.,Rutherford, George W.. Interventions to improve adherence to antiretroviral therapy in children with HIV infection. The Cochrane Library. 2011. #volume#:#pages#
26. Briggs, M. A.,Emerson, C.,Modi, S.,Taylor, N. K.,Date, A.. Use of isoniazid preventive therapy for tuberculosis prophylaxis among people living with HIV/AIDS: a review of the literature. J Acquir Immune Defic Syndr. 2015. 68 Suppl 3:S297-305
27. Brinkhof, M. W.,Pujades-Rodriguez, M.,Egger, M.. Mortality of patients lost to follow-up in antiretroviral treatment programmes in resource-limited settings: systematic review and meta-analysis. PLoS One. 2009. 4:e5790
28. Britto, C.,Mehta, K.,Thomas, R.,Shet, A.. Prevalence and Correlates of HIV Disclosure Among Children and Adolescents in Low- and Middle-Income Countries: A Systematic Review. J Dev Behav Pediatr. 2016. 37:496-505
29. Brown, Jennifer,Vanable,. Stress management interventions for HIV-infected individuals: review of recent intervention approaches and directions for future research. Neurobehavioral HIV Medicine. 2011. 3:95-106

30. Burch, L. S.,Smith, C. J.,Phillips, A. N.,Johnson, M. A.,Lampe, F. C.. Socioeconomic status and response to antiretroviral therapy in high-income countries: a literature review. AIDS. 2016. 30:1147-62
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Supplement 3: Characteristics of included studies

Study ID	Total studies (RCTs)	Key populations included	Intervention type	Target	Conclusion	Knowledge gaps	RoB
Amankwaa 2018[1]	13(13)	MSM, ACB	Digital	Adherence	Positive	Intervention	Low
Ambia 2016[2]	34(10)	ACB	Diverse	Retention	Positive	Design	Low
Anglada-Martinez 2015[3]	20(3)	MSM, ACB	Digital	Adherence	Positive	Design	Low
Arrivillaga 2013[4]	16(5)	ACB	Diverse	Adherence	Neutral	Population, Design	Unclear
Barnighausen 2011[5]	26(15)	ACB	Diverse	Adherence	Positive	Intervention	Low
Bateganya 2015[6]	20(1)	ACB	Behavioral	Retention	Positive	Population, Intervention	Unclear
Bhatta 2017[7]	28(28)	None	Diverse	Adherence	Neutral	Design	High
Bain-Brickley 2011[8]	4(2)	None	Diverse	Adherence	Neutral	Population	Low
Binford 2012[9]	45(15)	PWID	Behavioral	Adherence	Positive	Population	High
Brennan 2014[10]	5(5)	MSM, ACB	Health system	Retention	Positive	Design	High
Cao 2017[11]	26(8)	MSM, PWID, CSW	Digital	Retention	Positive	Population, Intervention	Low
Catalani 2013[12]	62(4)	MSM, Immigrants, CSW	Digital	Adherence	Positive	Evidence	High
Chaiyachati 2014[13]	124(19)	ACB, PWID	Diverse	Adherence	Positive	Population, Design	Low
Chang 2014[14]	12(9)	PWID	Behavioral	Adherence	Positive	Intervention, Design	Low
Charania 2014[15]	9(10)	MSM, ACB	Behavioral	Adherence	Positive	Evidence	Low
Checchi 2014[16]	37(34)	None	Digital	Adherence	Positive	Intervention, Design	Low
Cho 2017[17]	10(10)	MSM, ACB	Digital	Adherence	Indeterminate	Evidence, Outcome	Low
Claborn 2015[18]	10(6)	MSM, ACB, PWID, CSW	Digital	Adherence	Indeterminate	Intervention, Design	Low
Clay 2018[19]	63(34)	None	Medication modification	Adherence	Positive	Evidence	Low

Crepaz 2015[20]	15(15)	PWID	Health system	Adherence	Positive	Intervention	Low
Crepaz 2015[21]	15(8)	MSM, ACB, PWID	Diverse	Adherence	Positive	Evidence	High
Daher 2017[22]	99(38)	MSM, ACB, PWID, CSW	Digital	Retention	Positive	Population	Low
de Bruin 2010[23]	20(18)	ACB	Diverse	Adherence	Positive	Comparison	Low
de Jongh 2016[24]	12(2)	ACB	Diverse	Initiation	Positive	Evidence	Low
de Pee 2014[25]	10(0)	None	Economic	Adherence	Positive	Population, Design	Unclear
Decroo 2013[26]	18(2)	ACB	Peer or community based	Retention	Positive	Evidence	Unclear
Demonceau 2013[27]	79(30)	None	Diverse	Adherence	Positive	Design	Low
Feyissa 2014[28]	3(1)	ACB	Health system	Retention	Neutral	Evidence	Low
Ford 2009[29]	12(12)	ACB, PWID	Medication modification	Retention	Neutral	Intervention	Low
Ford 2018[30]	22(4)	MSM, ACB	Medication modification	Retention	Positive	Population	Low
Fox 2016[31]	22(10)	ACB	Diverse	Initiation	Neutral	Evidence	Low
Ganguli 2016[32]	64(8)	None	Diverse	Adherence	Positive	Intervention	Low
Gaston 2014[33]	13(4)	ACB	Diverse	Retention	Indeterminate	Evidence	High
Geldsetzer 2016[34]	10(4)	ACB	Digital	Retention	Positive	Evidence, Population	High
Genberg 2016[35]	9(8)	MSM, ACB	Peer or community based	Retention	Positive	Evidence, Intervention	Low
Govindasamy 2014[36]	24(5)	ACB, PWID	Diverse	Retention	Positive	Design	Low
Hart 2010[37]	17(11)	None	Medication modification	Adherence	Neutral	Design	Low
Herrmann 2017[38]	23(3)	PWID	Economic	Retention	Neutral	Evidence	High

Higa 2012[39]	13(4)	MSM, ACB, PWID	Diverse	Retention	Positive	Intervention, Design	Unclear
Higa 2016[40]	10(9)	None	Diverse	Retention	Positive	Evidence	Low
Higgs 2014[41]	26(4)	ACB	Digital	Adherence	Positive	Evidence	Unclear
Hill 2012[42]	5(5)	None	Diverse	Adherence	Positive	Evidence, Outcome	Low
Kanters 2016[43]	22(22)	MSM, ACB, PWID	Peer or community based	Adherence	Positive	Evidence, Design	Low
Kanters 2017[44]	85(87)	ACB, PWID	Diverse	Adherence	Positive	Population, Intervention, Design	Low
Keane 2017[45]	13(3)	ACB	Diverse	Retention	Positive	Intervention	Low
Knight 2018[46]	8(5)	ACB	Diverse	Retention	Indeterminate	Evidence, Population	Unclear
Kredo 2013[47]	16(2)	ACB	Health system	Retention	Positive	Design	Low
Kredo 2014[48]	10(4)	ACB	Task shifting	Retention	Positive	Population, Intervention, Design	Low
Lima 2016[49]	9(9)	ACB	Digital	Adherence	Positive	Intervention, Design	Low
Ma 2018[50]	23(9)	MSM, ACB	Diverse	Adherence	Positive	Design	High
MacPherson 2015[51]	11(3)	MSM, ACB	Diverse	Retention	Indeterminate	Population, Design	Low
Manias 2010[52]	46(9)	ACB, Immigrants	Diverse	Adherence	Positive	Intervention, Design	Low
Mathes 2013[53]	21(21)	None	Behavioral	Adherence	Neutral	Outcome, Design	Low
Mavegam 2017[54]	6(1)	ACB	Diverse	Retention	Positive	Evidence, Population	Low
Mayer 2017[55]	33(24)	MSM, ACB, PWID	Digital	Adherence	Positive	Population	High
Mbeye 2017[56]	3(3)	ACB	Pharmacy	Retention	Indeterminate	Evidence, Population, Intervention	Low
Mbuagbaw 2012[57]	28(4)	PWID	Behavioral	Adherence	Indeterminate	Evidence, Population	Low
Mbuagbaw 2015[58]	49(49)	MSM, ACB	Diverse	Adherence	Neutral	Population, Intervention, Design	Low
Medley 2015[59]	92(11)	MSM, ACB	Diverse	Retention	Positive	Population, Intervention	High

Mills 2014[60]	14(14)	ACB	Digital	Adherence	Positive	Population, Intervention	High
Mizuno 2018[61]	20(5)	PWID	Diverse	Retention	Positive	Design	Low
Muessig 2015[62]	23(21)	MSM, ACB, PWID	Digital	Retention	Indeterminate	Evidence	High
Murray 2017[63]	23(2)	ACB	Diverse	Retention	Indeterminate	Population	Unclear
Musayon-Oblitas 2018[64]	9 (9)	None	Behavioral	Adherence	Positive	Evidence, Intervention	Low
Mutasa-Apollo 2017[65]	11(3)	ACB	Health system	Retention	Positive	Evidence	Low
Nachega 2016[66]	22(11)	MSM, PWID, CSW	Peer or community based	Retention	Positive	Population, Design	Low
Parienti 2009[67]	11(11)	None	Medication modification	Adherence	Positive	None	High
Park 2014[68]	29(5)	MSM	Digital	Adherence	Positive	Intervention	Low
Perazzo 2017[69]	6(4)	MSM, PWID	Diverse	Adherence	Positive	Evidence	Unclear
Purnomo 2018[70]	16(7)	MSM, PWID, CSW	Digital	Retention	Positive	Design	Low
Quintana 2018[71]	26(19)	ACB	Digital	Retention	Neutral	Population, Intervention	Low
Ramjan 2014[72]	21(6)	ACB	Medication modification	Adherence	Positive	Evidence	Low
Ridgeway 2018[73]	52(29)	ACB	Diverse	Adherence	Positive	Population	Low
Riley 2015[74]	11 (6)	MSM, ACB	Behavioral	Adherence	Positive	Evidence, Intervention, Comparison	High
Risher 2017[75]	152(14)	MSM, PWID	Diverse	Retention	Positive	Evidence, Population, Intervention, Design	Low
Robbins 2014[76]	10(12)	MSM, ACB	Diverse	Adherence	Indeterminate	Population, Intervention, Design	Unclear
Rocha 2015[77]	4(4)	None	Pharmacy	Adherence	Neutral	Design	Low
Rueda 2006[78]	19(19)	MSM, ACB, PWID, Immigrants	Diverse	Adherence	Positive	Outcome, Design	Low

Ruzagira 2017[79]	14(3)	ACB	Peer or community based	Initiation	Neutral	Design	Low
Saberi 2011[80]	36(3)	None	Digital	Adherence	Positive	Intervention	Low
Saberi 2012[81]	32(2)	MSM, ACB	Pharmacy	Adherence	Positive	Intervention	Low
Scott-Sheldon 2017[82]	21(21)	ACB	Diverse	Adherence	Positive	Intervention	Low
Sharma 2016[83]	126(6)	MSM, ACB	Peer or community based	Retention	Positive		Low
Shaw 2016[84]	10(3)	MSM, ACB	Diverse	Adherence	Positive	Population, Design	High
Suthar 2017[85]	4(1)	ACB	Economic	Retention	Positive	Evidence	Low
Swann 2018[86]	38(9)	ACB, PWID	Economic	Retention	Positive	Evidence, Design	High
Tang 2015[87]	21(5)	ACB	Diverse	Retention	Indeterminate	Evidence, Intervention	High
van Camp 2013[88]	10(7)	ACB	Task shifting	Adherence	Positive	Design	Unclear
van der Heijden 2017[89]	16(19)	MSM, ACB	Behavioral	Adherence	Neutral	Evidence, Population	Low
van Velthoven 2012[90]	9(9)	PWID	Digital	Adherence	Neutral	Population	Low
van Velthoven 2013[91]	21(4)	ACB	Digital	Adherence	Neutral	Design	High
Vervloet 2012[92]	13(5)	None	Digital	Adherence	Positive	Population, Intervention	Low
Vojnov 2016[93]	30(3)	ACB	Health system	Initiation	Positive	Evidence	Low
Wise 2008[94]	21(8)	None	Digital	Adherence	Indeterminate	Evidence, Design	High
Wouters 2012[95]	29(7)	ACB	Peer or community based	Adherence	Positive	Design	Unclear
Wynberg 2014[96]	15(1)	ACB, Immigrants	Health system	Retention	Neutral	Intervention	Low
Yang 2014[97]	11(11)	None	Diverse	Adherence	Positive	Design	Unclear

Young 2010[98]	13(13)	ACB	Peer or community based	Retention	Positive	Evidence, Population	Low

ACB: African, Caribbean and Black people; CSW: commercial sex workers; MSM: men who have sex with men; PWID: people who inject drugs; RCTs: randomized controlled trials; RoB: risk of bias.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	online supplementary appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	online supplementary appendix 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	online supplementary appendix 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8 (figure 3)
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10-11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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