




BMJ Open 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 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 (MSM), African, Caribbean and Black (ACB) people, sex workers (SWs), people who inject drugs (PWID) and indigenous people). We searched PubMed, Excerpta Medica dataBASE, Cumulative Index to Nursing and Allied Health Literature, 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 ACB (66/98; 67.3%), MSM (32/98; 32.7%), PWID (6/98; 6.1%), SWs and prisoners (both 4/98; 4.1%). Interventions were: mixed (37/98; 37.8%), digital (22/98; 22.4%), behavioural 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 effective (69/98; 70.4%), 17.3% (17/98) were neutral or were indeterminate 12.2% (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 categorisation 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 categorised 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 targets³ 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 programmes 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 subpopulations.^{7,8} The literature suggests that vulnerable populations such as men who have sex with men (MSM), sex workers (SWs), 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 world 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 suggest 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 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 target, 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 71 000 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 randomised trials included in the systematic reviews.

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.

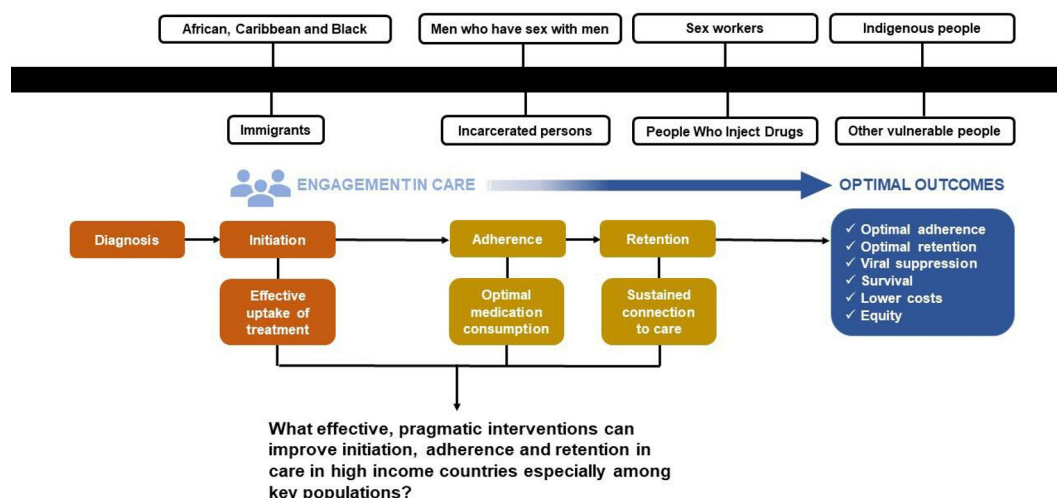


Figure 1 Outline of the HIV care cascade.

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 Organisations/Community-Based Organisations. Decision makers and representatives from the Ministry of Health and Long-Term Care of Ontario were also consulted.

Criteria for considering reviews for inclusion

We included any systematic reviews with at least one study with a randomised 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 (eg, attention control, usual care, another intervention) 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, Excerpta Medica dataBASE, Cumulative Index to Nursing and Allied Health Literature, PsycINFO, Web of Science and the Cochrane Library; from 1995 (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 supplemental file (online supplemental appendix 1).

We also searched the websites of the WHO, UNAIDS, National Institute for Health and Care Excellence and the systematic review database housed at the OHTN: Synthesised HIV/AIDS Research Evidence (<http://www.hivevidence.ca/frnSearch.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 onto 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 second 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 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 (ie, initiation, adherence, retention) and the intervention types: behavioural 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.

Conclusion statements were categorised 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 organised to inform different parts of the decision-making process, and interventions can be related to governance, financial or delivery arrangements.²⁹ Intervention 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 2420 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

Table 1 Categorisation of intervention types in the systematic reviews

Intervention category	Types
Behavioural and 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	Homebased 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

systematic reviews is provided as a supplemental file (online supplemental appendix 2).

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 52 58–60 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) randomised 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 (ACB) 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}

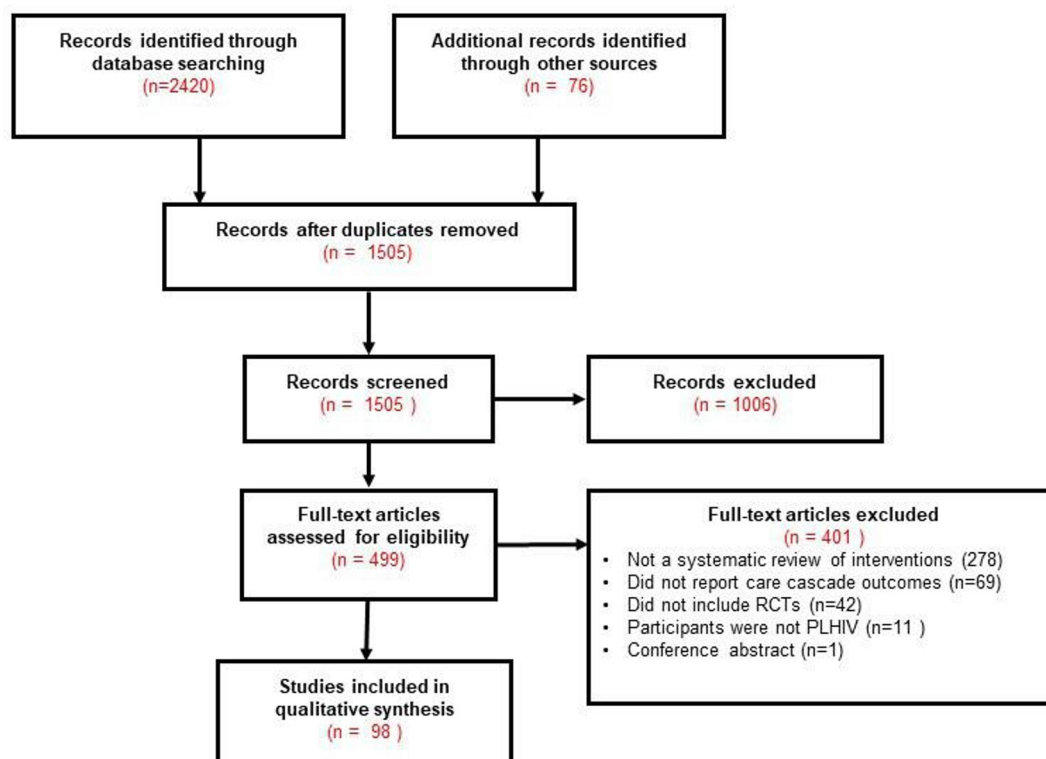


Figure 2 Systematic review flow diagram. PLHIV, people living with HIV; RCTs, randomised controlled trials.

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 randomised 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)
Behavioural 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.

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 supplemental appendix 3).

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 two 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 supplemental appendix 3).

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 supplemental file (online supplemental 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-based or community-based interventions^{65 113} improved initiation of ART. Two systematic reviews at high or unclear risk of bias reported that digital⁶⁴ 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 behavioural/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-based^{86 111} and task-shifting interventions⁷⁷ improved adherence to ART. Eighteen (18/21.9%) systematic reviews at high or unclear risk of bias reported that behavioural/educational,^{39 104} digital,^{42 71 85 90} mixed,^{50 80 89 99 114 127} economic,^{55 68 116} medication modification,⁹⁷ peer-based or community-based¹²⁵ and task-shifting¹¹⁸ 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-shifting⁷⁷ interventions improved adherence to HIV care. Seven (7/17.9%) of systematic reviews at high or unclear risk of bias reported that behavioural/educational,³⁷ digital,⁶⁴ mixed,^{70 89} economics,¹¹⁶ health system⁴⁰ and peer-based

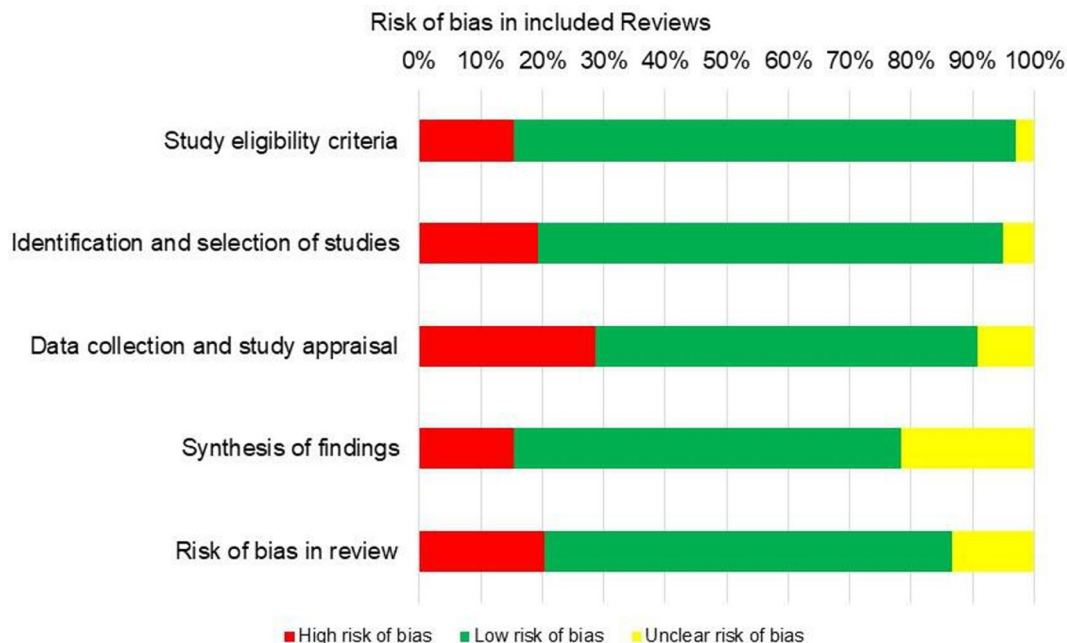


Figure 3 Risk of bias summary.

or community-based interventions⁵⁶ 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 marginalised groups such as children, youth, MSM, pregnant and breastfeeding 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) randomised 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 did not 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

Evidence maps of HIV care cascade interventions

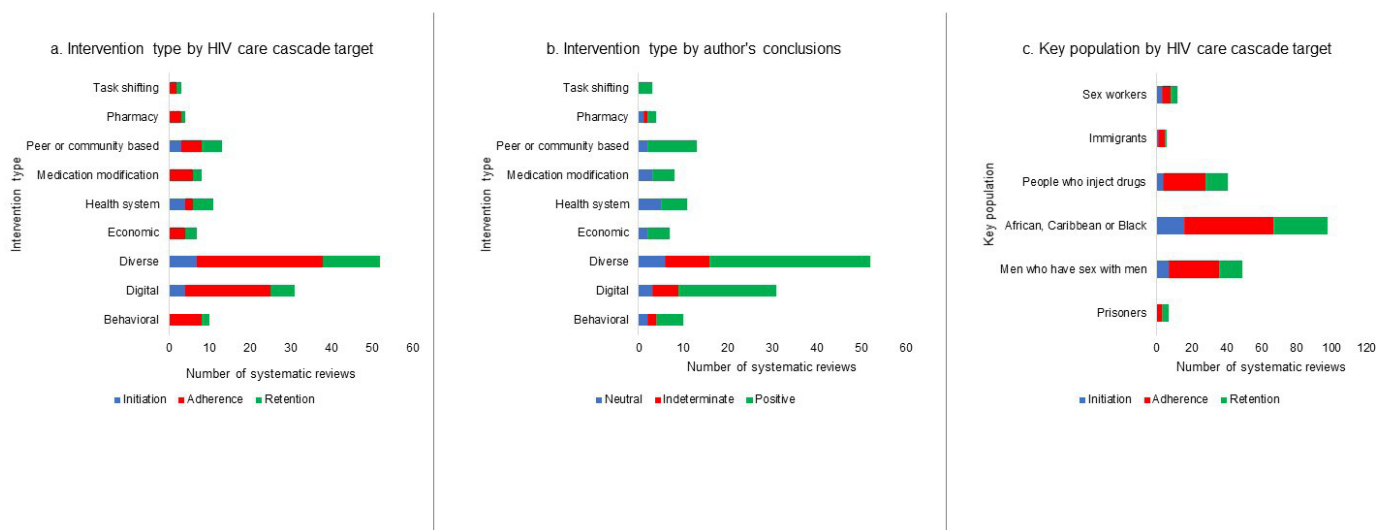


Figure 4 Evidence maps of HIV care cascade interventions.

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-based 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) 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 populations¹²⁹ and challenges with scaling-up interventions.¹³⁰

The disproportionate study of adherence might be due to its 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 to describe the breadth of definitions used for both adherence and retention. Standardised definitions are important for jurisdictions to be able to measure changes over time and make cross jurisdictional comparisons. Standardised definitions will also help systematic reviewers to synthesise 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. Second, 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 enrich 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 vs 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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