BMJ Open

Strategies to improve adherence to antiretroviral therapy and retention in care for people living with HIV: a protocol for an overview of systematic reviews

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022982
Article Type:	Protocol
Date Submitted by the Author:	15-Mar-2018
Complete List of Authors:	Mbuagbaw, Lawrence; McMaster University, Department of Health Research Methods, Evidence and Impact; Father Sean O'Sullivan Research Centre, St Joseph's Healthcare Hamilton, Biostatistics Unit Mertz, Dominik; McMaster University, Medicine Lawson, Daeria; McMaster University, Department of Health Research Methods, Evidence and Impact; University Health Network, Rheumatology Department Smieja, Marek; McMaster University, Department of Clinical Epidemiology and Biostatistics Benoit, Anita; Women's College Research Institute; University of Toronto Dalla Lana School of Public Health Alvarez, Elizabeth; McMaster University, Health Research Methods, Evidence and Impact; McMaster University, Centre for Health Economics and Policy Analysis (CHEPA) Puchalski Ritchie, Lisa; University of Toronto, Medicine; University Health Network, Department of Emergency Medicine Rachlis, Beth; Ontario HIV Treatment Network; Dignitas International Logie, Carmen; University of Toronto, Factor-Inwentash Faculty of Social Work; University of Toronto, Women's College Research Institute Husbands, Winston; Ontario HIV Treatment Network Margolese, Shari; Canadian HIV Trials Network Community Advisory Committee Thabane, Lehana ; McMaster University, Health Research Methods, Evidence and Impact
Keywords:	antiretroviral therapy, HIV, adherence, retention, pragmatic

Strategies to improve adherence to antiretroviral therapy and retention in care for people living with HIV: a protocol for an overview of systematic reviews

Authors:

Lawrence Mbuagbaw[1,2,3*], Dominik Mertz[1,4], Daeria Lawson[1], Marek Smieja[1,4], Anita C. Benoit[5,6], Elizabeth Alvarez[1,7], Lisa Puchalski Ritchie[8,9], Beth Rachlis[11, 12, 13] Carmen Logie[14], Winston Husbands[11], Shari Margolese[15], Lehana Thabane[1,2,16, 17, 18]

Affiliations:

[1]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada; [2]Biostatistics Unit, Father Sean O'Sullivan Research Centre, St Joseph's Healthcare, Hamilton, ON, Canada; [3]Centre for Development of Best Practices in Health (CDBPH), Yaoundé Central Hospital, Yaoundé, Cameroon; [4]Department of Medicine, McMaster University, Hamilton, ON, Canada; [5]Women's College Research Institute, Toronto, ON, Canada; [6]Dalla Lana School of Public Health, University of Toronto, ON, Canada; [7]Centre for Health Economics and Policy Analysis (CHEPA), McMaster University, Hamilton, ON, Canada; [8]Department of Medicine, University of Toronto, Toronto, ON, Canada; [9]Department of Emergency Medicine, University Health Network, Toronto, ON, Canada; [10]Li Ka Shing Knowledge Institute, St. Michaels Hospital, Toronto, ON, Canada; [11]The Ontario HIV Treatment Network, Toronto, ON, Canada; [12]Dignitas International, Toronto, ON Canada; [13]Division of Clinical Public Health, Dalla Lana School of Toronto, University of Toronto, Toronto, ON, Canada; [14]Factor-Inwentash Faculty of Social Work, University of Toronto, Toronto, ON, Canada; [15]Canadian HIV Trials Network Community Advisory

Committee; [16]Departments of Paediatrics and Anaesthesia, McMaster University, Hamilton, ON, Canada; [17]Centre for Evaluation of Medicine, St Joseph's Healthcare Hamilton, ON, Canada; [18] Population Health Research Institute, Hamilton Health Sciences, Hamilton, ON, Canada.

Email addresses: *Lawrence Mbuagbaw:mbuagblc@mcmaster.ca; Dominik Mertz: mertzd@mcmaster.ca; Daeria Lawson:lawsod3@mcmaster.ca; Marek Smieja: smiejam@mcmaster.ca; Anita C. Benoit: anita.benoit@utoronto.ca; Elizabeth Alvarez: alvare@mcmaster.ca; Lisa Puchalski Ritchie: lisapuchalskiritchi@utoronto.ca; Beth Rachlis: brachlis@ohtn.ca; Carmen Logie: carmen.logie@utoronto.ca; Winston Husbands: whusbands@ohtn.ca; Shari Margolese: shari.margolese@gmail.com; Lehana Thabane: thabanl@mcmaster.ca.

*Corresponding author:

Biostatistics Unit/FSORC, 50 Charlton Avenue East

St Joseph's Healthcare—Hamilton, 3rd Floor Martha Wing, Room H321

Hamilton, Ontario L8N 4A6, CANADA

Tel: 1-905-522-1155 ext 35929

Fax: 1-905-528-7386

Key words:

HIV, antiretroviral therapy, adherence, retention, pragmatic

Word count: 2586

Abstract

Introduction

While access to antiretroviral therapy (ART) for people living with HIV has expanded in recent years, additional efforts are required to support adherence to medication and retention in care. Interventions should be applicable in real-world settings and amenable to widespread use. The objectives of this overview are to identify effective pragmatic interventions that increase adherence to ART and retention in care for people living with HIV at high risk for suboptimal adherence and retention in high income countries.

Methods and analysis

We will conduct an overview of systematic reviews of studies on interventions which target improved adherence to medication and retention in care among people with HIV in high income. We will search 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. We will conduct screening, data extraction and assessment of methodological quality of the systematic reviews. Analysis will be narrative. Our findings will be interpreted in light of the certainty of the evidence, level of pragmatism, setting and population of interest.

Ethics and dissemination:

Only published secondary data will be used in this study and therefore ethics approval is not required. Our findings will be disseminated as peer-reviewed manuscripts, conference

abstracts and through community activities. The findings from this overview will inform a mixed methods study among people with HIV and health workers in Ontario, Canada.

Article Summary:

Article focus

- An outline of the procedures for an overview of systematic reviews of interventions to improve adherence to antiretroviral therapy and retention in care in high income countries

Key message

- An overview of systematic reviews can provide insight into the most appropriate interventions to enhance adherence to medication and retention in care among people living with HIV in high income countries

Strengths and limitations

- An exhaustive and comprehensive search strategy
- Findings will be interpreted in light of levels of pragmatism of interventions and quality of evidence
- Trials not included in systematic reviews will not be evaluated

Introduction:

More than 37 million people are living with human immunodeficiency virus (HIV) worldwide as of 2017.[1] Even though the number of new infections is decreasing, the number of people living with HIV is on the rise.[2] This is because individuals are living longer and healthier lives, mostly as a result of effective antiretroviral therapy (ART).[2] When taken as prescribed, ART reduces viral load and facilitates immune reconstitution. However, adherence to ART is often suboptimal.[3] This leads to worse and costly treatment outcomes (treatment switches due to development of resistance to first-line agents, more hospitalisations and death). [4-6] The increased longevity of people living with HIV implies that they would have to take medication for longer, and therefore strategies should be put in place to support adherence and retention in care over the life-time of the individual. Even though more recent evidence suggests that lower levels of adherence (~85% of pills) may still lead to viral suppression, [7,8] the highest levels of adherence are recommended to ensure optimal clinical and biological outcomes, as well as to prevent development of resistance and onward transmission of the virus [9,10]

Adherence to medication, defined as the "extent to which patients take medications as prescribed by their health care provider" or more broadly as "the extent to which a person's behaviour—taking medication, following a diet, or executing lifestyle changes - corresponds with agreed recommendations from a health care provider" is a complex phenomenon.[11,12] The first definition only describes compliance to specifications from the provider, whereas the later includes all recommendations jointly agreed upon by both parties. Adherence is known to be linked to patient factors such as age, depression, level of

education, social factors (such as level of social support, stigma), medication factors (such as pill burden, type of drug, side-effects), provider-related factors (quality of provider-patient relationship, trust, satisfaction with care), disease characteristics (stage of disease), clinical setting including where care is located, and other health system factors, such as funding for treatments.[13-16]

Retention in care (or continued care) is essential to adherence. However, retention in care is more challenging to define as there is no gold standard.[17] Some authors have proposed "remaining connected to medical care, once entered" as a working definition. With regards to HIV, retention has been defined as "patients known to be alive and receiving treatment, " or based on the frequency of clinic visits (varying from 2 weeks to 1 year), [18] or the number of viral load tests conducted each year.[19]

In high-income countries like Canada, injection drug use, homelessness and sex work are factors associated with sub-optimal adherence. [20] In addition, low self-efficacy, co-morbid psychiatric conditions and female gender are also linked to lower rates of adherence [21,22], as are younger age (<40 years), drug use, Indigenous ethnicity and hazardous drinking or smoking status.[19,23] These findings indicate that adherence to ART and retention in care in Canada are profoundly shaped by the social contexts of patients' lives.

This is contrary to developing countries, where in addition to these social factors, poverty, access to medication, comorbid diseases and health system factors play a larger role.[24] For example, out-of-pocket payment for health care, poor transportation infrastructure and stock outs may hamper regular consumption of medication. Retention in

care is a necessary element for adherence to medication, as patients must be connected to medical care to receive clinical, pharmaceutical and laboratory care. In a Canadian cohort of people living with HIV, only 7.5% of people living with HIV had a gap in care (no care for up to one year) over a period of 2 years, but up to 20% had suboptimal levels of retention (only one visit per year instead of two).[19]

If up to 20% of the 37 million people with HIV have sub-optimal or discontinuous care, more than 7 million people in the world may be more likely to fail treatment, develop resistant strains, transmit the virus, and experience poor clinical outcomes and reduced quality and quantity of life. [25]

The need to rethink HIV care strategies to improve adherence and retention in care was recently highlighted in a cost-effectiveness model indicating that novel approaches to engage and retain patients in care are critical. The authors estimate that improved retention will reduce HIV incidence by 54% and mortality by 64% with a cost-effectiveness ratio of $45,300 per QALY gained.[26]

In the field of adherence to ART and retention in care among people living with HIV, a number of effective interventions have been identified that improve adherence or clinical outcomes and retention in care. However, scaling up such interventions has been challenging due to the levels of complexity (multiple interconnecting parts), the resources required and challenges in teasing out the “essential” ingredient of multicomponent interventions. In addition, these interventions did not often address the needs of subpopulations at high risk of poor adherence or discontinued care, and were often designed for implementation (and tested) in low-and-middle-income settings only, and

may therefore be less applicable to high risk populations in high income country contexts. [27]

The purpose of this overview is to inform policies in high-income countries on strategies to improve adherence to antiretroviral therapy (ART) and retention in care. Our objectives are to:

1. Summarise the evidence on pragmatic (applicable in broad routine clinical practice as opposed to controlled research settings) and effective adherence or retention enhancing interventions among priority populations (men who have sex with men [MSM], African, Caribbean and Black people [ACB], women at risk [including sex workers], people who inject drugs, indigenous peoples] and other socially marginalised groups (immigrants, refugees and people with precarious immigration status) of people living with HIV.
2. Identify knowledge gaps in intervention research with regards to medication adherence for the different populations for further research.

This overview will be guided by the following questions:

1. What interventions have been demonstrated to improve adherence to therapy or retention in care for people (adults and children) living with HIV?
2. How pragmatic are these interventions in terms of participant characteristics, trial setting, flexibility of interventions, and clinical relevance of interventions?
3. Which interventions are adapted for subpopulations such as ACB populations, MSM, Indigenous populations, women at risk, people who use drugs (injection and non-

injection), younger people, immigrants, refugees and people with precarious immigration status?

4. What resources (people, equipment, money) are needed for implementation of these interventions?

Why it is important to do this overview of systematic reviews:

There is uncertainty in the most effective interventions for adherence and retention in HIV care in high income settings. For example, a recent systematic review in World Health Organisation (WHO) stratum A (a list of countries including Canada and the USA with very low child mortality and low adult mortality) found that most interventions had no effect or did not improve both adherence and clinical outcomes. [28] On the other hand, a US-based study identified a number of effective interventions (for adherence) including interactive discussions, pager messages and home visits. [29] Further, ten best practices for improving linkage and retention to care including case management and use of motivational interviewing were identified in a 2016 systematic review, although the authors noted that more rigorous study designs were needed to evaluate their effectiveness.[30] A recent scoping review reported that integrating HIV services with other services is beneficial to care, retention and adherence.[31] However, it is unclear which interventions are most effective, applicable to specific settings or populations and can be implemented on a large scale.

To answer these questions we will conduct an overview of systematic reviews to compile evidence from multiple systematic reviews into an accessible document in order to guide and add power to decision making.[32] Therefore, in this review we will critically appraise

the current literature, explore how to incorporate our findings into usual practice and support health worker and policy decisions regarding choice of intervention.

Methods:

This work is an overview of systematic reviews and will be guided by standard Cochrane methods.[33]

Criteria for considering systematic reviews for inclusion

We will include systematic reviews (with predetermined objectives, eligibility criteria, at least two databases searched, data extraction, and quality assessment of included studies) that include at least one study that reports on a randomized comparison of an intervention designed to improve adherence to ART or retention in care as defined by the investigators. We will exclude abstracts, non-systematic reviews and other overviews.

Search methods for identification of systematic reviews

We will conduct 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. These data bases will be searched from 1995 (when combination ART was introduced) to present. [34] No language restrictions will be set. A search strategy will be developed in collaboration with a Librarian from the Health Sciences Centre Library at McMaster University and a Cochrane Trial Search Coordinator which will be adapted for each database. The search strategy will be appraised by an independent librarian using PRESS (Peer Review of

Electronic Search Strategies) guidelines.[35] The following terms in various combinations (and forms) will be used for the search:

"Systematic review OR meta-analysis; Randomiz(s)ed OR RCT OR trials; Adherence OR compliance OR retention OR nonadheren OR uncompliant* OR treatment refusal OR persistence OR non-persistence; 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"*

The bibliographies of identified reviews will be searched. In order to find grey literature, we will search institutional websites such as the World Health Organisation (WHO), the National Institute for Health and Care Excellence (NICE), and the Joint United Nations Programme on HIV/AIDS (UNAIDS). Experts in the field of HIV adherence and retention will be approached to help identify other relevant articles.

Systematic review selection, data collection and analysis

The results of the search will be collated in Endnote reference manager. [36] Duplicate citations will be removed, then the remaining references will be screened for relevance based on their titles and abstracts by at least two reviewers working independently (LM, DL). Full text copies of the potentially relevant titles will be screened against our inclusion criteria. Data from the included studies will be extracted using a piloted data extraction from. The following types of information will be extracted: date of publication, number and type of included studies, number of participants, type of participants, study setting (country and clinic type), type of intervention(s), resources used, measures of adherence and retention used, and other effectiveness measures. Article screening and data extraction

will be conducted in duplicate. Agreement on screening and inclusion will be measured using the Kappa statistic,[37] and discrepancies will be resolved by discussion or arbitration (LT). Non-English studies will be screened by colleagues at McMaster University who speak and read French, Chinese, Spanish, German and Italian, or by crowdsourcing with the global Cochrane community. As needed, authors of systematic review or trials will be contacted for clarifications or missing information. The key characteristics of included studies will be reported in a table of included studies. The excluded studies and the reasons for exclusion will also be reported in a table. We will assess the risk of bias in the included systematic reviews using the ROBIS tool. [38] This tool can be used to appraise systematic reviews in three phases: assessing the relevance of the question, identifying concerns with the review process and judging risk of bias. As such a systematic review may be judged to be at high, low or unclear risk of bias. [38] The included systematic reviews will be checked for overlap of studies, since one study may appear in more than one review. The review will be reported according to the PRISMA statement.[39] Findings will be reported on the systematic review level (aggregated findings) and on the individual study level.

Analysis and interpretation

We will conduct narrative analyses. We will create a list of the most effective interventions, including their settings, target populations, category of adherence/retention issue addressed (patient, medication, provider-related, disease, clinical setting and other health system factors) the relative and absolute measures of effect. For an intervention to be considered effective, it should improve either adherence or retention measures and at least

one clinical or laboratory outcome e.g. viral load. The certainty of the evidence will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, which categorises each outcome by how confident we are that the effect estimate is close to the quantity of interest.[40] Using this approach the certainty rating across studies can be high, moderate, low or very low. Then we will use the RITES (Rating of Included Trials on the Efficacy-Effectiveness Spectrum) tool to appraise how pragmatic these interventions are.[41] With this tool, trials can be rated on a five-point Likert scale in four domains: (1) participant characteristics, (2) trial setting, (3) flexibility of interventions, and (4) clinical relevance of interventions. For each of these domains a score of 1 (very explanatory –strong emphasis on efficacy) to 5 (very pragmatic –strong emphasis on effectiveness) can be allocated. [41] This tool is specifically designed for post-hoc appraisal of clinical trials. The resources requirements and "burden" of the intervention will be noted (e.g. number of staff, skill set, hours per week, cost, number of patient visits, internet use, literacy level of users). GRADE and RITES tools will be used in duplicate by data extractors working independently.

The findings will be interpreted with consideration of the populations that are at high risk of poor adherence and retention: MSM, ACB men and women, Indigenous men and women, individuals who use drugs, and women who face systemic risk, and other groups known to have challenges with engagement in care. Notes will be made as to whether the interventions were tested in these populations and demonstrated to be effective.

Strengths and limitations:

This protocol has one limitation. Trials not already included in systematic reviews will not be evaluated. Some strengths include the use a comprehensive and exhaustive search strategy to identify effective and pragmatic interventions, appraisal of the quality of evidence and a multidisciplinary team.

Ethics and dissemination:

Only published secondary data will be used in this study and therefore ethics approval is not required. We plan to publish at least two peer reviewed manuscripts, and to submit results to international and national conferences such as the Canadian Association for HIV Research (CAHR), the OHTN Research Conference and the International AIDS Society (IAS) conferences. The findings from this overviews will inform a mixed methods study among health care workers and people living with HIV on the challenges and facilitators to implementing adherence and retention enhancing strategies.

Author Contributions:

LM developed the first draft of the manuscript. EA, DL, BR, MS, DM, LPR, CL, SM, AB, WH and LT revised several versions of the manuscript and approved the final version.

Funding statement:

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests statement:

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

Data statement:

Not applicable

Acknowledgements:

None

References:

1. UNAIDS. Fact sheet - Latest statistics on the status of the AIDS epidemic. Secondary Fact sheet - Latest statistics on the status of the AIDS epidemic 2017. http://www.unaids.org/en/resources/fact-sheet.
2. UNAIDS. AIDS by the numbers 2015. Secondary AIDS by the numbers 2015 2016. http://www.unaids.org/sites/default/files/media_asset/AIDS-by-the-numbers-2016_en.pdf.
3. Ortego C, Huedo-Medina TB, Llorca J, et al. Adherence to highly active antiretroviral therapy (HAART): a meta-analysis. AIDS Behav 2011;**15**(7):1381-96 doi: 10.1007/s10461-011-9942-x[published Online First: Epub Date]|.
4. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med 2000;**133**(1):21-30 doi: 200007040-00004 [pii][published Online First: Epub Date]|.
5. Bangsberg DR, Perry S, Charlebois ED, et al. Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. AIDS 2001;**15**(9):1181-3
6. Garcia de Olalla P, Knobel H, Carmona A, Guelar A, Lopez-Colomes JL, Cayla JA. Impact of adherence and highly active antiretroviral therapy on survival in HIV-infected patients. J Acquir Immune Defic Syndr 2002;**30**(1):105-10
7. Bangsberg DR. Less Than 95% Adherence to Nonnucleoside Reverse-Transcriptase Inhibitor Therapy Can Lead to Viral Suppression. Clinical Infectious Diseases 2006;**43**(7):939-41 doi: 10.1086/507526[published Online First: Epub Date]|.
8. Apisarnthanarak A, Mundy LM. Long-Term Outcomes of HIV-Infected Patients with <95% Rates of Adherence to Nonnucleoside Reverse-Transcriptase Inhibitors. Clinical Infectious Diseases 2010;**51**(1):115-17 doi: 10.1086/653445[published Online First: Epub Date]|.
9. Haubrich RH, Little SJ, Currier JS, et al. The value of patient-reported adherence to antiretroviral therapy in predicting virologic and immunologic response. California Collaborative Treatment Group. AIDS 1999;**13**(9):1099-107
10. Mannheimer S, Friedland G, Matts J, Child C, Chesney M. The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons in clinical trials. Clin Infect Dis 2002;**34**(8):1115-21 doi: CID010623 [pii]

10.1086/339074[published Online First: Epub Date]|.
11. Blaschke TF, Osterberg L, Vrijens B, Urquhart J. Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. Annu Rev Pharmacol Toxicol 2012;**52**:275-301 doi: 10.1146/annurev-pharmtox-011711-113247[published Online First: Epub Date]|.
12. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;**353**(5):487-97 doi: 353/5/487 [pii]

10.1056/NEJMra050100[published Online First: Epub Date]|.

13. WHO. Adherence to long-term therapies: Evidence for action. Secondary Adherence to long-term therapies: Evidence for action 2003. http://www.who.int/chp/knowledge/publications/adherence_report/en/.
14. Logie CH, Lacombe-Duncan A, Wang Y, et al. Pathways From HIV-Related Stigma to Antiretroviral Therapy Measures in the HIV Care Cascade for Women Living With HIV in Canada. JAIDS Journal of Acquired Immune Deficiency Syndromes 2018;**77**(2):144-53 doi: 10.1097/qai.0000000000001589[published Online First: Epub Date]|.
15. Hodgson I, Plummer ML, Konopka SN, et al. A systematic review of individual and contextual factors affecting ART initiation, adherence, and retention for HIV-infected pregnant and postpartum women. PLoS One 2014;**9**(11):e111421 doi: 10.1371/journal.pone.0111421[published Online First: Epub Date]|.
16. Katz IT, Ryu AE, Onuegbu AG, et al. Impact of HIV-related stigma on treatment adherence: systematic review and meta-synthesis. J Int AIDS Soc 2013;**16**(3 Suppl 2):18640 doi: 10.7448/ias.16.3.18640[published Online First: Epub Date]|.
17. Mugavero MJ, Westfall AO, Zinski A, et al. Measuring retention in HIV care: the elusive gold standard. J Acquir Immune Defic Syndr 2012;**61**(5):574-80 doi: 10.1097/QAI.0b013e318273762f[published Online First: Epub Date]|.
18. Geng EH, Nash D, Kambugu A, et al. Retention in Care Among HIV-Infected Patients in Resource-Limited Settings: Emerging Insights and New Directions. Current HIV/AIDS reports 2010;**7**(4):234-44 doi: 10.1007/s11904-010-0061-5[published Online First: Epub Date]|.
19. Rachlis B, Burchell AN, Gardner S, et al. Social determinants of health and retention in HIV care in a clinical cohort in Ontario, Canada. AIDS Care 2017;**29**(7):828-37 doi: 10.1080/09540121.2016.1271389[published Online First: Epub Date]|.
20. Joseph B, Kerr T, Puskas CM, Montaner J, Wood E, Milloy MJ. Factors linked to transitions in adherence to antiretroviral therapy among HIV-infected illicit drug users in a Canadian setting. AIDS Care 2015;**27**(9):1128-36 doi: 10.1080/09540121.2015.1032205[published Online First: Epub Date]|.
21. Kerr T, Palepu A, Barness G, et al. Psychosocial determinants of adherence to highly active antiretroviral therapy among injection drug users in Vancouver. Antivir Ther 2004;**9**(3):407-14
22. Tapp C, Milloy M-J, Kerr T, et al. Female gender predicts lower access and adherence to antiretroviral therapy in a setting of free healthcare. BMC Infectious Diseases 2011;**11**(1):1-7 doi: 10.1186/1471-2334-11-86[published Online First: Epub Date]|.
23. Lourenco L, Nohpal A, Shopin D, et al. Non-HIV-related health care utilization, demographic, clinical and laboratory factors associated with time to initial retention in HIV care among HIV-positive individuals linked to HIV care. HIV Med 2016;**17**(4):269-79 doi: 10.1111/hiv.12297[published Online First: Epub Date]|.
24. Mbuagbaw L, Thabane L, Ongolo-Zogo P, et al. Trends and determining factors associated with adherence to antiretroviral therapy (ART) in Cameroon: a systematic review and analysis of the CAMPS trial. AIDS Research and Therapy 2012;**9**:37-37 doi: 10.1186/1742-6405-9-37[published Online First: Epub Date]|.
25. Skarbinski J, Rosenberg E, Paz-Bailey G, et al. Human immunodeficiency virus transmission at each step of the care continuum in the United States. JAMA internal medicine 2015;**175**(4):588-96 doi: 10.1001/jamainternmed.2014.8180[published Online First: Epub Date]|.

26. Shah M, Risher K, Berry SA, Dowdy DW. The Epidemiologic and Economic Impact of Improving HIV Testing, Linkage, and Retention in Care in the United States. Clin Infect Dis 2016;**62**(2):220-9 doi: 10.1093/cid/civ801[published Online First: Epub Date]|.
27. Mbuagbaw L, Sivaramalingam B, Navarro T, et al. Interventions for Enhancing Adherence to Antiretroviral Therapy (ART): A Systematic Review of High Quality Studies. AIDS Patient Care and STDs 2015 doi: 10.1089/apc.2014.0308[published Online First: Epub Date]|.
28. Mathes T, Pieper D, Antoine SL, Eikermann M. Adherence-enhancing interventions for highly active antiretroviral therapy in HIV-infected patients - a systematic review. HIV Med 2013;**14**(10):583-95 doi: 10.1111/hiv.12051[published Online First: Epub Date]|.
29. Charania MR, Marshall KJ, Lyles CM, et al. Identification of Evidence-Based Interventions for Promoting HIV Medication Adherence: Findings from a Systematic Review of U.S.-Based Studies, 1996-2011. AIDS Behav 2013 doi: 10.1007/s10461-013-0594-x[published Online First: Epub Date]|.
30. Higa DH, Crepaz N, Mullins MM. Identifying Best Practices for Increasing Linkage to, Retention, and Re-engagement in HIV Medical Care: Findings from a Systematic Review, 1996–2014. AIDS and Behavior 2016;**20**(5):951-66 doi: 10.1007/s10461-015-1204-x[published Online First: Epub Date]|.
31. Heard A, Peterson K, Modi S, Esper H, Calvo F, Brown AN. Integrating HIV services with other health services to improve care, retention and adherence. 3ie Scoping Report 7. New Delhi: International Initiative for Impact Evaluation (3ie), 2017.
32. Silva V, Grande AJ, Carvalho APVd, Martimbianco ALC, Riera R. Overview of systematic reviews - a new type of study. Part II. Sao Paulo Medical Journal 2015;**133**:206-17
33. Becker LA, Oxman AD. Overviews of reviews. Cochrane handbook for systematic reviews of interventions: Cochrane book series 2008:607-31
34. Palmisano L, Vella S. A brief history of antiretroviral therapy of HIV infection: success and challenges. Annali dell'Istituto superiore di sanitÃ 2011;**47**(1):44-48
35. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;**75**:40-6 doi: 10.1016/j.jclinepi.2016.01.021[published Online First: Epub Date]|.
36. Reuters T. EndNote X7. Thomson Reuters: Philadelphia, PA, USA 2013
37. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. Fam Med 2005;**37**(5):360-3
38. Whiting P, Savovic J, Higgins JP, et al. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol 2016;**69**:225-34 doi: 10.1016/j.jclinepi.2015.06.005[published Online First: Epub Date]|.
39. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;**8**(5):336-41 doi: 10.1016/j.ijsu.2010.02.007[published Online First: Epub Date]|.
40. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;**64**(4):383-94 doi: 10.1016/j.jclinepi.2010.04.026[published Online First: Epub Date]|.
41. Wieland LS, Berman BM, Altman DG, et al. Rating of Included Trials on the Efficacy-Effectiveness Spectrum: development of a new tool for systematic reviews. J Clin Epidemiol 2017;**84**:95-104 doi: 10.1016/j.jclinepi.2017.01.010[published Online First: Epub Date]|.

BMJ Open

Strategies to improve adherence to antiretroviral therapy and retention in care for people living with HIV in high-income countries: a protocol for an overview of systematic reviews

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022982.R1
Article Type:	Protocol
Date Submitted by the Author:	22-Jun-2018
Complete List of Authors:	Mbuagbaw, Lawrence; McMaster University, Department of Health Research Methods, Evidence and Impact; Father Sean O'Sullivan Research Centre, St Joseph's Healthcare Hamilton, Biostatistics Unit Mertz, Dominik; McMaster University, Medicine Lawson, Daeria; McMaster University, Department of Health Research Methods, Evidence and Impact; University Health Network, Rheumatology Department Smieja, Marek; McMaster University, Department of Clinical Epidemiology and Biostatistics Benoit, Anita; Women's College Research Institute; University of Toronto Dalla Lana School of Public Health Alvarez, Elizabeth; McMaster University, Health Research Methods, Evidence and Impact; McMaster University, Centre for Health Economics and Policy Analysis (CHEPA) Puchalski Ritchie, Lisa; University of Toronto, Medicine; University Health Network, Department of Emergency Medicine Rachlis, Beth; Ontario HIV Treatment Network; Dignitas International Logie, Carmen; University of Toronto, Factor-Inwentash Faculty of Social Work; University of Toronto, Women's College Research Institute Husbands, Winston; Ontario HIV Treatment Network Margolese, Shari; Canadian HIV Trials Network Community Advisory Committee Thabane, Lehana ; McMaster University, Health Research Methods, Evidence and Impact
Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	Health services research, Public health
Keywords:	antiretroviral therapy, HIV, adherence, retention, pragmatic

Strategies to improve adherence to antiretroviral therapy and retention in care for people living with HIV in high income countries: a protocol for an overview of systematic reviews

Authors:

Lawrence Mbuagbaw[1,2,3*], Dominik Mertz[1,4], Daeria Lawson[1], Marek Smieja[1,4], Anita C. Benoit[5,6], Elizabeth Alvarez[1,7], Lisa Puchalski Ritchie[8,9], Beth Rachlis[11, 12, 13] Carmen Logie[14], Winston Husbands[11], Shari Margolese[15], Lehana Thabane[1,2,16, 17, 18]

Affiliations:

[1]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada; [2]Biostatistics Unit, Father Sean O'Sullivan Research Centre, St Joseph's Healthcare, Hamilton, ON, Canada; [3]Centre for Development of Best Practices in Health (CDBPH), Yaoundé Central Hospital, Yaoundé, Cameroon; [4]Department of Medicine, McMaster University, Hamilton, ON, Canada; [5]Women's College Research, Toronto, ON, Canada; [6]Dalla Lana School of Public Health, University of Toronto, ON, Canada; [7]Centre for Health Economics and Policy Analysis (CHEPA), McMaster University, Hamilton, ON, Canada; [8]Department of Medicine, University of Toronto, Toronto, ON, Canada; [9]Department of Emergency Medicine, University Health Network, Toronto, ON, Canada; [10]Li Ka Shing Knowledge Institute, St. Michaels Hospital, Toronto, ON, Canada; [11]The Ontario HIV Treatment Network, Toronto, ON, Canada; [12]Dignitas International, Toronto, ON Canada; [13]Division of Clinical Public Health, Dalla Lana School of Toronto, University of Toronto, Toronto, ON, Canada; [14]Factor-Inwentash Faculty of Social Work, University of Toronto, Toronto, ON, Canada; [15]Canadian HIV Trials Network Community Advisory

Committee; [16]Departments of Paediatrics and Anaesthesia, McMaster University, Hamilton, ON, Canada; [17]Centre for Evaluation of Medicine, St Joseph's Healthcare Hamilton, ON, Canada; [18] Population Health Research Institute, Hamilton Health Sciences, Hamilton, ON, Canada.

Email addresses: *Lawrence Mbuagbaw:mbuagblc@mcmaster.ca; Dominik Mertz: mertzd@mcmaster.ca; Daeria Lawson:lawsod3@mcmaster.ca; Marek Smieja: smiejam@mcmaster.ca; Anita Benoit: anita.beniot@utoronto.ca; Elizabeth Alvarez: alvare@mcmaster.ca; Lisa Puchalski Ritchie: lisapuchalskiritchi@utoronto.ca; Beth Rachlis: brachlis@ohtn.ca; Carmen Logie: carmen.logie@utoronto.ca; Winston Husbands: whusbands@ohtn.ca; Shari Margolese: shari.margolese@gmail.com; Lehana Thabane: thabanl@mcmaster.ca.

*Corresponding author:

Biostatistics Unit/FSORC, 50 Charlton Avenue East

St Joseph's Healthcare—Hamilton, 3rd Floor Martha Wing, Room H321

Hamilton, Ontario L8N 4A6, CANADA

Tel: 1-905-522-1155 ext 35929

Fax: 1-905-528-7386

Key words:

HIV, antiretroviral therapy, adherence, retention, pragmatic

Word count: 2586

Abstract

Introduction

While access to antiretroviral therapy (ART) for people living with HIV has expanded in recent years, additional efforts are required to support adherence to medication and retention in care. Interventions should be applicable in real-world settings and amenable to widespread use. The objectives of this overview are to identify effective pragmatic interventions that increase adherence to ART and retention in care for people living with HIV at high risk for suboptimal adherence and retention in high income countries.

Methods and analysis

We will conduct an overview of systematic reviews of studies on interventions which target improved adherence to medication and retention in care among high risk people living with HIV in high-income countries (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 will search 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. We will conduct screening, data extraction and assessment of methodological quality of the systematic reviews. Analysis will be narrative. Our findings will be interpreted in light of the certainty of the evidence, level of pragmatism, setting and population of interest.

Ethics and dissemination:

Only published secondary data will be used in this study and therefore ethics approval is not required. Our findings will be disseminated as peer-reviewed manuscripts, conference abstracts and through community activities. The findings from this overview will inform a mixed methods study among people living with HIV and health workers in Ontario, Canada.

Strengths and limitations

- An exhaustive and comprehensive search strategy
- Findings will be interpreted in the light of levels of pragmatism and quality of evidence
- Trials not yet included in systematic reviews will not be evaluated

Introduction:

More than 37 million people are living with human immunodeficiency virus (HIV) worldwide as of 2017.[1] Even though the number of new infections is decreasing, the number of people living with HIV is on the rise.[2] This is because individuals are living longer and healthier lives, mostly as a result of effective antiretroviral therapy (ART).[2] When taken as prescribed, ART reduces viral load and facilitates immune reconstitution.[3] However, adherence to ART is often suboptimal.[4] This leads to worse and costly treatment outcomes (treatment switches due to development of resistance to first-line agents, more hospitalisations and death). [3,5,6] The increased longevity of people living with HIV implies that they would have to take medication for longer, and therefore strategies should be put in place to support adherence and retention in care over the life-time of the individual. Even though more recent evidence suggests that lower levels of adherence (~85% of pills) may still lead to viral suppression, [7,8] the highest levels of adherence are recommended to ensure optimal clinical and biological outcomes, as well as to prevent development of resistance and onward transmission of the virus [9,10]

Adherence to medication, defined as the "extent to which patients take medications as prescribed by their health care provider" or more broadly as "the extent to which a person's behaviour—taking medication, following a diet, or executing lifestyle changes - corresponds with agreed recommendations from a health care provider" is a complex phenomenon.[11,12] The first definition only describes compliance to specifications from the provider, whereas the later includes all recommendations jointly agreed upon by both parties. Adherence is known to be linked to patient factors such as age, depression, level of

education, social factors (such as level of social support, stigma), medication factors (such as pill burden, type of drug, side-effects), provider-related factors (quality of provider-patient relationship, trust, satisfaction with care), disease characteristics (stage of disease), clinical setting including where care is located, and other health system factors, such as funding for treatments.[13,14] [15,16]

Retention in care (or continued care) is essential to adherence. However, retention in care is more challenging to define as there is no gold standard.[17] Some authors have proposed "remaining connected to medical care, once entered" as a working definition. With regards to HIV, retention has been defined as "patients known to be alive and receiving treatment, " or based on the frequency of clinic visits (varying from 2 weeks to 1 year), [18] or the number of viral load tests conducted each year.[19]

In high-income countries like Canada, injection drug use, homelessness and sex work are factors associated with sub-optimal adherence. [20] In addition, low self-efficacy, co-morbid psychiatric conditions and female gender are also linked to lower rates of adherence [21,22], as are younger age (<40 years), drug use, Indigenous ethnicity and hazardous drinking or smoking status.[19,23] These findings indicate that adherence to ART and retention in care in Canada are profoundly shaped by the social contexts of patients' lives.

This is contrary to developing countries, where in addition to these social factors, poverty, access to medication, comorbid diseases and health system factors play a larger role.[24] For example, out-of-pocket payment for health care, poor transportation infrastructure and stock outs may hamper regular consumption of medication. Retention in

care is a necessary element for adherence to medication, as patients must be connected to medical care to receive clinical, pharmaceutical and laboratory care. In a Canadian cohort of people living with HIV, only 7.5% of people living with HIV had a gap in care (no care for up to one year) over a period of 2 years, but up to 20% had suboptimal levels of retention (only one visit per year instead of two).[19]

If up to 20% of the 37 million people living with HIV have sub-optimal or discontinuous care, more than 7 million people in the world may be more likely to fail treatment, develop resistant strains, transmit the virus, and experience poor clinical outcomes and reduced quality and quantity of life. [25]

The need to rethink HIV care strategies to improve adherence and retention in care was recently highlighted in a cost-effectiveness model indicating that novel approaches to engage and retain patients in care are critical. The authors estimate that improved retention will reduce HIV incidence by 54% and mortality by 64% with a cost-effectiveness ratio of $45,300 per QALY gained.[26]

In the field of adherence to ART and retention in care among people living with HIV, a number of effective interventions have been identified that improve adherence or clinical outcomes and retention in care.[18,27] However, scaling up such interventions has been challenging due to the levels of complexity (multiple interconnecting parts), the resources required and challenges in teasing out the “essential” ingredient of multicomponent interventions.[28,29] In addition, these interventions did not often address the needs of subpopulations at high risk of poor adherence or discontinued care, and were often designed for implementation (and tested) in low-and-middle-income settings only, and

may therefore be less applicable to high risk populations in high income country contexts. [27]

The purpose of this overview is to inform policies in high-income countries on strategies to improve adherence to antiretroviral therapy (ART) and retention in care. Our objectives are to:

1. Summarise the evidence on pragmatic (applicable in broad routine clinical practice as opposed to controlled research settings) and effective adherence or retention enhancing interventions among priority populations (men who have sex with men [MSM], African, Caribbean and Black people [ACB], women at risk [including sex workers], people who inject drugs, indigenous peoples] and other socially marginalised groups (immigrants, refugees and people with precarious immigration status) of people living with HIV. These are groups identified to be at high risk of discontinuing treatment in Ontario.
2. Identify knowledge gaps in intervention research with regards to medication adherence and retention for the different populations of interest.

This overview will be guided by the following questions:

1. What interventions have been demonstrated to improve adherence to therapy or retention in care for people (adults and children) living with HIV?
2. How pragmatic are these interventions in terms of participant characteristics, trial setting, flexibility of interventions, and clinical relevance of interventions?

3. Which interventions are adapted for subpopulations such as MSM, ACB populations, women at risk, people who use drugs (injection and non-injection), Indigenous populations and other marginalised groups (immigrants, refugees and people with precarious immigration status)?
4. What resources (people, equipment, money) are needed for implementation of these interventions?

There is uncertainty in the most effective interventions for adherence and retention in HIV care in high income settings. For example, a recent systematic review in World Health Organisation (WHO) stratum A (a list of countries including Canada and the USA with very low child mortality and low adult mortality) found that most interventions had no effect or did not improve both adherence and clinical outcomes. [30] On the other hand, a US-based study identified a number of effective interventions (for adherence) including interactive discussions, pager messages and home visits. [31] Further, ten best practices for improving linkage and retention to care including case management and use of motivational interviewing were identified in a 2016 systematic review, although the authors noted that more rigorous study designs were needed to evaluate their effectiveness.[32] A recent scoping review reported that integrating HIV services with other services is beneficial to care, retention and adherence.[33] However, it is unclear which interventions are most effective, applicable to specific settings or populations and can be implemented on a large scale.

To answer these questions we will conduct an overview of systematic reviews to compile evidence from multiple systematic reviews into an accessible document in order to guide

and add power to decision making.[34] Therefore, in this review we will critically appraise the current literature, explore how to incorporate our findings into usual practice and support health worker and policy decisions regarding choice of intervention.

Methods:

This work is an overview of systematic reviews and will be guided by standard Cochrane methods.[35]

Patient and Public involvement:

This research question was formulated based on HIV management priorities identified by the Ontario HIV Treatment Network (OHTN), which specifically aims to close gaps in the care cascade by improving adherence to medication and retention in care. The author team includes patients, representatives of community based organisations, care providers and researchers who are involved in the design and implementation of this project.

Criteria for considering systematic reviews for inclusion

We will include systematic reviews (with predetermined objectives, eligibility criteria, at least two databases searched, data extraction, and quality assessment of included studies) that include at least one study that reports on a randomized comparison of an intervention designed to improve adherence to ART or retention in care as defined by the investigators. We will exclude abstracts, non-systematic reviews and other overviews.

Search methods for identification of systematic reviews

We will conduct 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. These data bases will be searched from 1995 (when combination ART was introduced) to present. [36] No language restrictions will be set. A search strategy will be developed in collaboration with a Librarian from the Health Sciences Centre Library at McMaster University and a Cochrane Trial Search Coordinator which will be adapted for each database. The search strategy will be appraised by an independent librarian using PRESS (Peer Review of Electronic Search Strategies) guidelines.[37] The following terms in various combinations (and forms) will be used for the search:

"Systematic review OR meta-analysis; 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; 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"*

The bibliographies of identified reviews will be searched. In order to find grey literature, we will search institutional websites such as the World Health Organisation (WHO), the National Institute for Health and Care Excellence (NICE), and the Joint United Nations Programme on HIV/AIDS (UNAIDS). Experts in the field of HIV adherence and retention will be approached to help identify other relevant articles.

Systematic review selection and data collection

The results of the search will be collated in Endnote reference manager. [38] Duplicate citations will be removed, then the remaining references will be screened for relevance based on their titles and abstracts by at least two reviewers working independently (LM, DL). Full text copies of the potentially relevant titles will be screened against our inclusion criteria. Data from the included studies will be extracted using a piloted data extraction form. The following types of information will be extracted: date of publication, number and type of included studies, number of participants, type of participants, study setting (country and clinic type), type of intervention(s), resources used, measures of adherence and retention used (as defined by the authors), and other effectiveness measures. Country income level will be defined as per World Bank criteria.[39] Article screening and data extraction will be conducted in duplicate. Agreement on screening and inclusion will be measured using the Kappa statistic,[40] and discrepancies will be resolved by discussion or arbitration (LT). Non-English studies will be screened by colleagues at McMaster University who speak and read French, Chinese, Spanish, German and Italian, or by crowdsourcing with the global Cochrane community. As needed, authors of systematic review or trials will be contacted for clarifications or missing information. The key characteristics of included studies will be reported in a table of included studies. The excluded studies and the reasons for exclusion will also be reported in a table. We will assess the risk of bias in the included systematic reviews using the ROBIS tool. [41] This tool can be used to appraise systematic reviews in three phases: assessing the relevance of the question, identifying concerns with the review process and judging risk of bias. As such a systematic review may be judged to be at high, low or unclear risk of bias. [41] The included systematic reviews will be checked for overlap of studies, since one study may

appear in more than one review. The review will be reported according to the PRISMA statement.[42] Findings will be reported on the systematic review level (aggregated findings) and on the individual study level. Only data from randomized comparisons will be used.

Analysis and interpretation

We will conduct narrative analyses. We will create a list of the most effective interventions, including their settings, target populations, category of adherence/retention issue addressed (patient, medication, provider-related, disease, clinical setting and other health system factors) the relative and absolute measures of effect. For an intervention to be considered effective, it should improve either adherence or retention measures and at least one clinical or laboratory outcome e.g. viral load. Studies that do not include clinical measures will be included, but considered as indirect evidence. The certainty of the evidence will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, which categorises each outcome by how confident we are that the effect estimate is close to the quantity of interest.[43] Using this approach the certainty rating across studies can be high, moderate, low or very low. Then we will use the RITES (Rating of Included Trials on the Efficacy-Effectiveness Spectrum) tool to appraise how pragmatic these interventions are.[44] With this tool, trials can be rated on a five-point Likert scale in four domains: (1) participant characteristics, (2) trial setting, (3) flexibility of interventions, and (4) clinical relevance of interventions. For each of these domains a score of 1 (very explanatory –strong emphasis on efficacy) to 5 (very pragmatic –strong emphasis on effectiveness) can be allocated. [44] This tool is specifically

designed for post-hoc appraisal of clinical trials. The resources requirements and "burden" of the intervention will be noted (e.g. number of staff, skill set, hours per week, cost, number of patient visits, internet use, literacy level of users). GRADE and RITES tools will be used in duplicate by data extractors working independently.

The findings will be interpreted with consideration of the populations that are at high risk of poor adherence and retention: MSM, ACB men and women, Indigenous men and women, individuals who use drugs, and women who face systemic risk, and other groups known to have challenges with engagement in care. Notes will be made as to whether the interventions were tested in these populations and demonstrated to be effective.

Ethics and dissemination:

Only published secondary data will be used in this study and therefore ethics approval is not required. We plan to publish at least two peer reviewed manuscripts, and to submit results to international and national conferences such as the Canadian Association for HIV Research (CAHR), the OHTN Research Conference and the International AIDS Society (IAS) conferences. The findings from this overviews will inform a mixed methods study among health care workers and people living with HIV on the challenges and facilitators to implementing adherence and retention enhancing strategies. These findings will respond to identified HIV management concerns in Ontario and will provide insights into how to support adherence to medication and retention in care among high risk populations in high-income countries, especially Canada.

Author Contributions:

LM developed the first draft of the manuscript. EA, DL, BR, MS, DM, LPR, CL, SM, AB, WH and LT revised several versions of the manuscript and approved the final version. LM is the guarantor of the protocol.

Funding statement:

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests statement:

The authors declare none.

References:

1. UNAIDS. Fact sheet - Latest statistics on the status of the AIDS epidemic. Secondary Fact sheet - Latest statistics on the status of the AIDS epidemic 2017. http://www.unaids.org/en/resources/fact-sheet.
2. UNAIDS. AIDS by the numbers 2015. Secondary AIDS by the numbers 2015 2016. http://www.unaids.org/sites/default/files/media_asset/AIDS-by-the-numbers-2016_en.pdf.
3. Bangsberg DR, Perry S, Charlebois ED, et al. Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. AIDS 2001;**15**(9):1181-3
4. Ortego C, Huedo-Medina TB, Llorca J, et al. Adherence to highly active antiretroviral therapy (HAART): a meta-analysis. AIDS Behav 2011;**15**(7):1381-96 doi: 10.1007/s10461-011-9942-x[published Online First: Epub Date]|.
5. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med 2000;**133**(1):21-30 doi: 200007040-00004 [pii][published Online First: Epub Date]|.
6. Garcia de Olalla P, Knobel H, Carmona A, Guelar A, Lopez-Colomes JL, Cayla JA. Impact of adherence and highly active antiretroviral therapy on survival in HIV-infected patients. J Acquir Immune Defic Syndr 2002;**30**(1):105-10

7. Bangsberg DR. Less Than 95% Adherence to Nonnucleoside Reverse-Transcriptase Inhibitor Therapy Can Lead to Viral Suppression. Clinical Infectious Diseases 2006;**43**(7):939-41 doi: 10.1086/507526[published Online First: Epub Date]|.
8. Apisarnthanarak A, Mundy LM. Long-Term Outcomes of HIV-Infected Patients with <95% Rates of Adherence to Nonnucleoside Reverse-Transcriptase Inhibitors. Clinical Infectious Diseases 2010;**51**(1):115-17 doi: 10.1086/653445[published Online First: Epub Date]|.
9. Haubrich RH, Little SJ, Currier JS, et al. The value of patient-reported adherence to antiretroviral therapy in predicting virologic and immunologic response. California Collaborative Treatment Group. AIDS 1999;**13**(9):1099-107
10. Mannheimer S, Friedland G, Matts J, Child C, Chesney M. The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons in clinical trials. Clin Infect Dis 2002;**34**(8):1115-21 doi: CID010623 [pii]

10.1086/339074[published Online First: Epub Date]|.
11. Blaschke TF, Osterberg L, Vrijens B, Urquhart J. Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. Annu Rev Pharmacol Toxicol 2012;**52**:275-301 doi: 10.1146/annurev-pharmtox-011711-113247[published Online First: Epub Date]|.
12. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;**353**(5):487-97 doi: 353/5/487 [pii]

10.1056/NEJMra050100[published Online First: Epub Date]|.
13. WHO. Adherence to long-term therapies: Evidence for action. Secondary Adherence to long-term therapies: Evidence for action 2003. http://www.who.int/chp/knowledge/publications/adherence_report/en/.
14. Logie CH, Lacombe-Duncan A, Wang Y, et al. Pathways From HIV-Related Stigma to Antiretroviral Therapy Measures in the HIV Care Cascade for Women Living With HIV in Canada. JAIDS Journal of Acquired Immune Deficiency Syndromes 2018;**77**(2):144-53 doi: 10.1097/qai.0000000000001589[published Online First: Epub Date]|.
15. Hodgson I, Plummer ML, Konopka SN, et al. A systematic review of individual and contextual factors affecting ART initiation, adherence, and retention for HIV-infected pregnant and postpartum women. PLoS One 2014;**9**(11):e111421 doi: 10.1371/journal.pone.0111421[published Online First: Epub Date]|.
16. Katz IT, Ryu AE, Onuegbu AG, et al. Impact of HIV-related stigma on treatment adherence: systematic review and meta-synthesis. J Int AIDS Soc 2013;**16**(3 Suppl 2):18640 doi: 10.7448/ias.16.3.18640[published Online First: Epub Date]|.
17. Mugavero MJ, Westfall AO, Zinski A, et al. Measuring retention in HIV care: the elusive gold standard. J Acquir Immune Defic Syndr 2012;**61**(5):574-80 doi: 10.1097/QAI.0b013e318273762f[published Online First: Epub Date]|.
18. Geng EH, Nash D, Kambugu A, et al. Retention in Care Among HIV-Infected Patients in Resource-Limited Settings: Emerging Insights and New Directions. Current HIV/AIDS reports 2010;**7**(4):234-44 doi: 10.1007/s11904-010-0061-5[published Online First: Epub Date]|.

19. Rachlis B, Burchell AN, Gardner S, et al. Social determinants of health and retention in HIV care in a clinical cohort in Ontario, Canada. AIDS Care 2017;**29**(7):828-37 doi: 10.1080/09540121.2016.1271389[published Online First: Epub Date]|.
20. Joseph B, Kerr T, Puskas CM, Montaner J, Wood E, Milloy MJ. Factors linked to transitions in adherence to antiretroviral therapy among HIV-infected illicit drug users in a Canadian setting. AIDS Care 2015;**27**(9):1128-36 doi: 10.1080/09540121.2015.1032205[published Online First: Epub Date]|.
21. Kerr T, Palepu A, Barness G, et al. Psychosocial determinants of adherence to highly active antiretroviral therapy among injection drug users in Vancouver. Antivir Ther 2004;**9**(3):407-14
22. Tapp C, Milloy M-J, Kerr T, et al. Female gender predicts lower access and adherence to antiretroviral therapy in a setting of free healthcare. BMC Infectious Diseases 2011;**11**(1):1-7 doi: 10.1186/1471-2334-11-86[published Online First: Epub Date]|.
23. Lourenco L, Nohpal A, Shopin D, et al. Non-HIV-related health care utilization, demographic, clinical and laboratory factors associated with time to initial retention in HIV care among HIV-positive individuals linked to HIV care. HIV Med 2016;**17**(4):269-79 doi: 10.1111/hiv.12297[published Online First: Epub Date]|.
24. Mbuagbaw L, Thabane L, Ongolo-Zogo P, et al. Trends and determining factors associated with adherence to antiretroviral therapy (ART) in Cameroon: a systematic review and analysis of the CAMPS trial. AIDS Research and Therapy 2012;**9**:37-37 doi: 10.1186/1742-6405-9-37[published Online First: Epub Date]|.
25. Skarbinski J, Rosenberg E, Paz-Bailey G, et al. Human immunodeficiency virus transmission at each step of the care continuum in the United States. JAMA internal medicine 2015;**175**(4):588-96 doi: 10.1001/jamainternmed.2014.8180[published Online First: Epub Date]|.
26. Shah M, Risher K, Berry SA, Dowdy DW. The Epidemiologic and Economic Impact of Improving HIV Testing, Linkage, and Retention in Care in the United States. Clin Infect Dis 2016;**62**(2):220-9 doi: 10.1093/cid/civ801[published Online First: Epub Date]|.
27. Mbuagbaw L, Sivaramalingam B, Navarro T, et al. Interventions for Enhancing Adherence to Antiretroviral Therapy (ART): A Systematic Review of High Quality Studies. AIDS Patient Care and STDs 2015 doi: 10.1089/apc.2014.0308[published Online First: Epub Date]|.
28. Barker PM, Reid A, Schall MW. A framework for scaling up health interventions: lessons from large-scale improvement initiatives in Africa. Implement Sci 2016;**11**:12 doi: 10.1186/s13012-016-0374-x[published Online First: Epub Date]|.
29. Willis CD, Riley BL, Stockton L, et al. Scaling up complex interventions: insights from a realist synthesis. Health Res Policy Syst 2016;**14**(1):88 doi: 10.1186/s12961-016-0158-4[published Online First: Epub Date]|.
30. Mathes T, Pieper D, Antoine SL, Eikermann M. Adherence-enhancing interventions for highly active antiretroviral therapy in HIV-infected patients - a systematic review. HIV Med 2013;**14**(10):583-95 doi: 10.1111/hiv.12051[published Online First: Epub Date]|.
31. Charania MR, Marshall KJ, Lyles CM, et al. Identification of Evidence-Based Interventions for Promoting HIV Medication Adherence: Findings from a Systematic Review of U.S.-Based Studies, 1996-2011. AIDS Behav 2013 doi: 10.1007/s10461-013-0594-x[published Online First: Epub Date]|.

32. Higa DH, Crepaz N, Mullins MM. Identifying Best Practices for Increasing Linkage to, Retention, and Re-engagement in HIV Medical Care: Findings from a Systematic Review, 1996–2014. AIDS and Behavior 2016;**20**(5):951-66 doi: 10.1007/s10461-015-1204-x[published Online First: Epub Date]|.
33. Heard A, Peterson K, Modi S, Esper H, Calvo F, Brown AN. Integrating HIV services with other health services to improve care, retention and adherence. 3ie Scoping Report 7. New Delhi: International Initiative for Impact Evaluation (3ie), 2017.
34. Silva V, Grande AJ, Carvalho APVd, Martimbianco ALC, Riera R. Overview of systematic reviews - a new type of study. Part II. Sao Paulo Medical Journal 2015;**133**:206-17
35. Becker LA, Oxman AD. Overviews of reviews. Cochrane handbook for systematic reviews of interventions: Cochrane book series 2008:607-31
36. Palmisano L, Vella S. A brief history of antiretroviral therapy of HIV infection: success and challenges. Annali dell'Istituto superiore di sanitÃ 2011;**47**(1):44-48
37. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;**75**:40-6 doi: 10.1016/j.jclinepi.2016.01.021[published Online First: Epub Date]|.
38. Reuters T. EndNote X7. Thomson Reuters: Philadelphia, PA, USA 2013
39. Bank W. World Bank Open Data. Secondary World Bank Open Data 2018. https://data.worldbank.org/.
40. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. Fam Med 2005;**37**(5):360-3
41. Whiting P, Savovic J, Higgins JP, et al. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol 2016;**69**:225-34 doi: 10.1016/j.jclinepi.2015.06.005[published Online First: Epub Date]|.
42. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;**8**(5):336-41 doi: 10.1016/j.ijsu.2010.02.007[published Online First: Epub Date]|.
43. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;**64**(4):383-94 doi: 10.1016/j.jclinepi.2010.04.026[published Online First: Epub Date]|.
44. Wieland LS, Berman BM, Altman DG, et al. Rating of Included Trials on the Efficacy-Effectiveness Spectrum: development of a new tool for systematic reviews. J Clin Epidemiol 2017;**84**:95-104 doi: 10.1016/j.jclinepi.2017.01.010[published Online First: Epub Date]|.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	N/A
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1,2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	14
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	14
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5, 6, 7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	10
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	10, 11
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	11

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11, 12
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	12
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	12
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	11, 12
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	12
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	13
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	12, 13
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	N/A
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	13
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	N/A
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	13

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Strategies to improve adherence to antiretroviral therapy and retention in care for people living with HIV in high-income countries: a protocol for an overview of systematic reviews

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022982.R2
Article Type:	Protocol
Date Submitted by the Author:	17-Aug-2018
Complete List of Authors:	Mbuagbaw, Lawrence; McMaster University, Department of Health Research Methods, Evidence and Impact; Father Sean O'Sullivan Research Centre, St Joseph's Healthcare Hamilton, Biostatistics Unit Mertz, Dominik; McMaster University, Medicine Lawson, Daeria; McMaster University, Department of Health Research Methods, Evidence and Impact; University Health Network, Rheumatology Department Smieja, Marek; McMaster University, Department of Clinical Epidemiology and Biostatistics Benoit, Anita; Women's College Research Institute; University of Toronto Dalla Lana School of Public Health Alvarez, Elizabeth; McMaster University, Health Research Methods, Evidence and Impact; McMaster University, Centre for Health Economics and Policy Analysis (CHEPA) Puchalski Ritchie, Lisa; University of Toronto, Medicine; University Health Network, Department of Emergency Medicine Rachlis, Beth; Ontario HIV Treatment Network; Dignitas International Logie, Carmen; University of Toronto, Factor-Inwentash Faculty of Social Work; University of Toronto, Women's College Research Institute Husbands, Winston; Ontario HIV Treatment Network Margolese, Shari; Canadian HIV Trials Network Community Advisory Committee Thabane, Lehana ; McMaster University, Health Research Methods, Evidence and Impact
Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	Health services research, Public health
Keywords:	antiretroviral therapy, HIV, adherence, retention, pragmatic

Strategies to improve adherence to antiretroviral therapy and retention in care for people living with HIV in high-income countries: a protocol for an overview of systematic reviews

Authors:

Lawrence Mbuagbaw[1,2,3*], Dominik Mertz[1,4], Daeria Lawson[1], Marek Smieja[1,4], Anita C. Benoit[5,6], Elizabeth Alvarez[1,7], Lisa Puchalski Ritchie[8,9], Beth Rachlis[11, 12, 13] Carmen Logie[14], Winston Husbands[11], Shari Margolese[15], Lehana Thabane[1,2,16, 17, 18]

Affiliations:

[1]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada; [2]Biostatistics Unit, Father Sean O'Sullivan Research Centre, St Joseph's Healthcare, Hamilton, ON, Canada; [3]Centre for Development of Best Practices in Health (CDBPH), Yaoundé Central Hospital, Yaoundé, Cameroon; [4]Department of Medicine, McMaster University, Hamilton, ON, Canada; [5]Women's College Research, Toronto, ON, Canada; [6]Dalla Lana School of Public Health, University of Toronto, ON, Canada; [7]Centre for Health Economics and Policy Analysis (CHEPA), McMaster University, Hamilton, ON, Canada; [8]Department of Medicine, University of Toronto, Toronto, ON, Canada; [9]Department of Emergency Medicine, University Health Network, Toronto, ON, Canada; [10]Li Ka Shing Knowledge Institute, St. Michaels Hospital, Toronto, ON, Canada; [11]The Ontario HIV Treatment Network, Toronto, ON, Canada; [12]Dignitas International, Toronto, ON Canada; [13]Division of Clinical Public Health, Dalla Lana School of Toronto, University of Toronto, Toronto, ON, Canada; [14]Factor-Inwentash Faculty of Social Work, University of Toronto, Toronto, ON, Canada; [15]Canadian HIV Trials Network Community Advisory

Committee; [16]Departments of Paediatrics and Anaesthesia, McMaster University, Hamilton, ON, Canada; [17]Centre for Evaluation of Medicine, St Joseph's Healthcare Hamilton, ON, Canada; [18] Population Health Research Institute, Hamilton Health Sciences, Hamilton, ON, Canada.

Email addresses: *Lawrence Mbuagbaw:mbuagblc@mcmaster.ca; Dominik Mertz: mertzd@mcmaster.ca; Daeria Lawson:lawsod3@mcmaster.ca; Marek Smieja: smiejam@mcmaster.ca; Anita Benoit: anita.beniot@utoronto.ca; Elizabeth Alvarez: alvare@mcmaster.ca; Lisa Puchalski Ritchie: lisapuchalskiritchi@utoronto.ca; Beth Rachlis: brachlis@ohtn.ca; Carmen Logie: carmen.logie@utoronto.ca; Winston Husbands: whusbands@ohtn.ca; Shari Margolese: shari.margolese@gmail.com; Lehana Thabane: thabanl@mcmaster.ca.

*Corresponding author:

Biostatistics Unit/FSORC, 50 Charlton Avenue East

St Joseph's Healthcare—Hamilton, 3rd Floor Martha Wing, Room H321

Hamilton, Ontario L8N 4A6, CANADA

Tel: 1-905-522-1155 ext 35929

Fax: 1-905-528-7386

Key words:

HIV, antiretroviral therapy, adherence, retention, pragmatic

Word count: 2586

Abstract

Introduction

While access to antiretroviral therapy (ART) for people living with HIV has expanded in recent years, additional efforts are required to support adherence to medication and retention in care. Interventions should be applicable in real-world settings and amenable to widespread use. The objectives of this overview are to identify effective pragmatic interventions that increase adherence to ART and retention in care for people living with HIV at high risk for suboptimal adherence and retention in high income countries.

Methods and analysis

We will conduct an overview of systematic reviews of studies on interventions which target improved adherence to medication and retention in care among high risk people living with HIV in high-income countries (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 will search 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. We will conduct screening, data extraction and assessment of methodological quality of the systematic reviews. Analysis will be narrative. Our findings will be interpreted in light of the certainty of the evidence, level of pragmatism, setting and population of interest.

Ethics and dissemination:

Only published secondary data will be used in this study and therefore ethics approval is not required. Our findings will be disseminated as peer-reviewed manuscripts, conference abstracts and through community activities. The findings from this overview will inform a mixed methods study among people living with HIV and health workers in Ontario, Canada.

Strengths and limitations

- An exhaustive and comprehensive search strategy
- Findings will be interpreted in the light of levels of pragmatism and quality of evidence
- Trials not yet included in systematic reviews will not be evaluated

Introduction:

More than 37 million people are living with human immunodeficiency virus (HIV) worldwide as of 2017.[1] Even though the number of new infections is decreasing, the number of people living with HIV is on the rise.[2] This is because individuals are living longer and healthier lives, mostly as a result of effective antiretroviral therapy (ART).[2] When taken as prescribed, ART reduces viral load and facilitates immune reconstitution.[3] However, adherence to ART is often suboptimal.[4] This leads to worse and costly treatment outcomes (treatment switches due to development of resistance to first-line agents, more hospitalisations and death). [3,5,6] The increased longevity of people living with HIV implies that they would have to take medication for longer, and therefore strategies should be put in place to support adherence and retention in care over the life-time of the individual. Even though more recent evidence suggests that lower levels of adherence (~85% of pills) may still lead to viral suppression, [7,8] the highest levels of adherence are recommended to ensure optimal clinical and biological outcomes, as well as to prevent development of resistance and onward transmission of the virus [9,10]

Adherence to medication, defined as the "extent to which patients take medications as prescribed by their health care provider" or more broadly as "the extent to which a person's behaviour—taking medication, following a diet, or executing lifestyle changes - corresponds with agreed recommendations from a health care provider" is a complex phenomenon.[11,12] The first definition only describes compliance to specifications from the provider, whereas the later includes all recommendations jointly agreed upon by both parties. Adherence is known to be linked to patient factors such as age, depression, level of

education, social factors (such as level of social support, stigma), medication factors (such as pill burden, type of drug, side-effects), provider-related factors (quality of provider-patient relationship, trust, satisfaction with care), disease characteristics (stage of disease), clinical setting including where care is located, and other health system factors, such as funding for treatments.[13,14] [15,16]

Retention in care (or continued care) is essential to adherence. However, retention in care is more challenging to define as there is no gold standard.[17] Some authors have proposed "remaining connected to medical care, once entered" as a working definition. With regards to HIV, retention has been defined as "patients known to be alive and receiving treatment, " or based on the frequency of clinic visits (varying from 2 weeks to 1 year), [18] or the number of viral load tests conducted each year.[19]

In high-income countries like Canada, injection drug use, homelessness and sex work are factors associated with sub-optimal adherence. [20] In addition, low self-efficacy, co-morbid psychiatric conditions and female gender are also linked to lower rates of adherence [21,22], as are younger age (<40 years), drug use, Indigenous ethnicity and hazardous drinking or smoking status.[19,23] These findings indicate that adherence to ART and retention in care in Canada are profoundly shaped by the social contexts of patients' lives.

This is contrary to developing countries, where in addition to these social factors, poverty, access to medication, comorbid diseases and health system factors play a larger role.[24] For example, out-of-pocket payment for health care, poor transportation infrastructure and stock outs may hamper regular consumption of medication. Retention in

care is a necessary element for adherence to medication, as patients must be connected to medical care to receive clinical, pharmaceutical and laboratory care. In a Canadian cohort of people living with HIV, only 7.5% of people living with HIV had a gap in care (no care for up to one year) over a period of 2 years, but up to 20% had suboptimal levels of retention (only one visit per year instead of two).[19]

If up to 20% of the 37 million people living with HIV have sub-optimal or discontinuous care, more than 7 million people in the world may be more likely to fail treatment, develop resistant strains, transmit the virus, and experience poor clinical outcomes and reduced quality and quantity of life. [25]

The need to rethink HIV care strategies to improve adherence and retention in care was recently highlighted in a cost-effectiveness model indicating that novel approaches to engage and retain patients in care are critical. The authors estimate that improved retention will reduce HIV incidence by 54% and mortality by 64% with a cost-effectiveness ratio of $45,300 per QALY gained.[26]

In the field of adherence to ART and retention in care among people living with HIV, a number of effective interventions have been identified that improve adherence or clinical outcomes and retention in care.[18,27] However, scaling up such interventions has been challenging due to the levels of complexity (multiple interconnecting parts), the resources required and challenges in teasing out the “essential” ingredient of multicomponent interventions.[28,29] In addition, these interventions did not often address the needs of subpopulations at high risk of poor adherence or discontinued care, and were often designed for implementation (and tested) in low-and-middle-income settings only, and

may therefore be less applicable to high risk populations in high income country contexts. [27]

The purpose of this overview is to inform policies in high-income countries on strategies to improve adherence to antiretroviral therapy (ART) and retention in care. Our objectives are to:

1. Summarise the evidence on pragmatic (applicable in broad routine clinical practice as opposed to controlled research settings) and effective adherence or retention enhancing interventions among priority populations (men who have sex with men [MSM], African, Caribbean and Black people [ACB], women at risk [including sex workers], people who inject drugs, indigenous peoples] and other socially marginalised groups (immigrants, refugees and people with precarious immigration status) of people living with HIV. These are groups identified to be at high risk of discontinuing treatment in Ontario.
2. Identify knowledge gaps in intervention research with regards to medication adherence and retention for the different populations of interest.

This overview will be guided by the following questions:

1. What interventions have been demonstrated to improve adherence to therapy or retention in care for people (adults and children) living with HIV?
2. How pragmatic are these interventions in terms of participant characteristics, trial setting, flexibility of interventions, and clinical relevance of interventions?

3. Which interventions are adapted for subpopulations such as MSM, ACB populations, women at risk, people who use drugs (injection and non-injection), Indigenous populations and other marginalised groups (immigrants, refugees and people with precarious immigration status)?
4. What resources (people, equipment, money) are needed for implementation of these interventions?

There is uncertainty in the most effective interventions for adherence and retention in HIV care in high income settings. For example, a recent systematic review in World Health Organisation (WHO) stratum A (a list of countries including Canada and the USA with very low child mortality and low adult mortality) found that most interventions had no effect or did not improve both adherence and clinical outcomes. [30] On the other hand, a US-based study identified a number of effective interventions (for adherence) including interactive discussions, pager messages and home visits. [31] Further, ten best practices for improving linkage and retention to care including case management and use of motivational interviewing were identified in a 2016 systematic review, although the authors noted that more rigorous study designs were needed to evaluate their effectiveness.[32] A recent scoping review reported that integrating HIV services with other services is beneficial to care, retention and adherence.[33] However, it is unclear which interventions are most effective, applicable to specific settings or populations and can be implemented on a large scale.

To answer these questions we will conduct an overview of systematic reviews to compile evidence from multiple systematic reviews into an accessible document in order to guide

and add power to decision making.[34] Therefore, in this review we will critically appraise the current literature, explore how to incorporate our findings into usual practice and support health worker and policy decisions regarding choice of intervention.

Methods:

This work is an overview of systematic reviews and will be guided by standard Cochrane methods.[35]

Patient and Public involvement:

This research question was formulated based on HIV management priorities identified by the Ontario HIV Treatment Network (OHTN), which specifically aims to close gaps in the care cascade by improving adherence to medication and retention in care. The author team includes patients, representatives of community based organisations, care providers and researchers who are involved in the design and implementation of this project.

Criteria for considering systematic reviews for inclusion

We will include systematic reviews (with predetermined objectives, eligibility criteria, at least two databases searched, data extraction, and quality assessment of included studies) that include at least one study that reports on a randomized comparison of an intervention designed to improve adherence to ART or retention in care as defined by the investigators. We will exclude abstracts, non-systematic reviews and other overviews.

Search methods for identification of systematic reviews

We will conduct 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. These data bases will be searched from 1995 (when combination ART was introduced) to present. [36] No language restrictions will be set. A search strategy will be developed in collaboration with a Librarian from the Health Sciences Centre Library at McMaster University and a Cochrane Trial Search Coordinator which will be adapted for each database. The search strategy will be appraised by an independent librarian using PRESS (Peer Review of Electronic Search Strategies) guidelines.[37] The following terms in various combinations (and forms) will be used for the search:

"Systematic review OR meta-analysis; 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; 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"*

The bibliographies of identified reviews will be searched. In order to find grey literature, we will search institutional websites such as the World Health Organisation (WHO), the National Institute for Health and Care Excellence (NICE), and the Joint United Nations Programme on HIV/AIDS (UNAIDS). Experts in the field of HIV adherence and retention will be approached to help identify other relevant articles.

Systematic review selection and data collection

The results of the search will be collated in Endnote reference manager. [38] Duplicate citations will be removed, then the remaining references will be screened for relevance based on their titles and abstracts by at least two reviewers working independently (LM, DL). Full text copies of the potentially relevant titles will be screened against our inclusion criteria. Data from the included studies will be extracted using a piloted data extraction form. The following types of information will be extracted: date of publication, number and type of included studies, number of participants, type of participants, study setting (country and clinic type), type of intervention(s), resources used, measures of adherence and retention used (as defined by the authors), and other effectiveness measures. Country income level will be defined as per World Bank criteria.[39] Article screening and data extraction will be conducted in duplicate. Agreement on screening and inclusion will be measured using the Kappa statistic,[40] and discrepancies will be resolved by discussion or arbitration (LT). Non-English studies will be screened by colleagues at McMaster University who speak and read French, Chinese, Spanish, German and Italian, or by crowdsourcing with the global Cochrane community. As needed, authors of systematic review or trials will be contacted for clarifications or missing information. The key characteristics of included studies will be reported in a table of included studies. The excluded studies and the reasons for exclusion will also be reported in a table. We will assess the risk of bias in the included systematic reviews using the ROBIS tool. [41] This tool can be used to appraise systematic reviews in three phases: assessing the relevance of the question, identifying concerns with the review process and judging risk of bias. As such a systematic review may be judged to be at high, low or unclear risk of bias. [41] The included systematic reviews will be checked for overlap of studies, since one study may

appear in more than one review. The review will be reported according to the PRISMA statement.[42] Findings will be reported on the systematic review level (aggregated findings) and on the individual study level. Only data from randomized comparisons will be used.

Analysis and interpretation

We will conduct narrative analyses. We will create a list of the most effective interventions, including their settings, target populations, category of adherence/retention issue addressed (patient, medication, provider-related, disease, clinical setting and other health system factors) the relative and absolute measures of effect. For an intervention to be considered effective, it should improve either adherence or retention measures and at least one clinical or laboratory outcome e.g. viral load. Studies that do not include clinical measures will be included, but considered as indirect evidence. The certainty of the evidence will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, which categorises each outcome by how confident we are that the effect estimate is close to the quantity of interest.[43] Using this approach the certainty rating across studies can be high, moderate, low or very low. Then we will use the RITES (Rating of Included Trials on the Efficacy-Effectiveness Spectrum) tool to appraise how pragmatic these interventions are.[44] With this tool, trials can be rated on a five-point Likert scale in four domains: (1) participant characteristics, (2) trial setting, (3) flexibility of interventions, and (4) clinical relevance of interventions. For each of these domains a score of 1 (very explanatory –strong emphasis on efficacy) to 5 (very pragmatic –strong emphasis on effectiveness) can be allocated. [44] This tool is specifically

designed for post-hoc appraisal of clinical trials. The resources requirements and "burden" of the intervention will be noted (e.g. number of staff, skill set, hours per week, cost, number of patient visits, internet use, literacy level of users). GRADE and RITES tools will be used in duplicate by data extractors working independently.

The findings will be interpreted with consideration of the populations that are at high risk of poor adherence and retention: MSM, ACB men and women, Indigenous men and women, individuals who use drugs, and women who face systemic risk, and other groups known to have challenges with engagement in care. Notes will be made as to whether the interventions were tested in these populations and demonstrated to be effective.

Ethics and dissemination:

Only published secondary data will be used in this study and therefore ethics approval is not required. We plan to publish at least two peer reviewed manuscripts, and to submit results to international and national conferences such as the Canadian Association for HIV Research (CAHR), the OHTN Research Conference and the International AIDS Society (IAS) conferences. The findings from this overviews will inform a mixed methods study among health care workers and people living with HIV on the challenges and facilitators to implementing adherence and retention enhancing strategies. These findings will respond to identified HIV management concerns in Ontario and will provide insights into how to support adherence to medication and retention in care among high risk populations in high-income countries, especially Canada.

Author Contributions:

LM developed the first draft of the manuscript. EA, DL, BR, MS, DM, LPR, CL, SM, AB, WH and LT revised several versions of the manuscript and approved the final version. LM is the guarantor of the protocol.

Funding statement:

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests statement:

The authors declare none.

References:

1. UNAIDS. Fact sheet - Latest statistics on the status of the AIDS epidemic. Secondary Fact sheet - Latest statistics on the status of the AIDS epidemic 2017. http://www.unaids.org/en/resources/fact-sheet.
2. UNAIDS. AIDS by the numbers 2015. Secondary AIDS by the numbers 2015 2016. http://www.unaids.org/sites/default/files/media_asset/AIDS-by-the-numbers-2016_en.pdf.
3. Bangsberg DR, Perry S, Charlebois ED, et al. Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. AIDS 2001;**15**(9):1181-3
4. Ortego C, Huedo-Medina TB, Llorca J, et al. Adherence to highly active antiretroviral therapy (HAART): a meta-analysis. AIDS Behav 2011;**15**(7):1381-96 doi: 10.1007/s10461-011-9942-x[published Online First: Epub Date]|.
5. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med 2000;**133**(1):21-30 doi: 200007040-00004 [pii][published Online First: Epub Date]|.
6. Garcia de Olalla P, Knobel H, Carmona A, Guelar A, Lopez-Colomes JL, Cayla JA. Impact of adherence and highly active antiretroviral therapy on survival in HIV-infected patients. J Acquir Immune Defic Syndr 2002;**30**(1):105-10

7. Bangsberg DR. Less Than 95% Adherence to Nonnucleoside Reverse-Transcriptase Inhibitor Therapy Can Lead to Viral Suppression. Clinical Infectious Diseases 2006;**43**(7):939-41 doi: 10.1086/507526[published Online First: Epub Date]|.
8. Apisarnthanarak A, Mundy LM. Long-Term Outcomes of HIV-Infected Patients with <95% Rates of Adherence to Nonnucleoside Reverse-Transcriptase Inhibitors. Clinical Infectious Diseases 2010;**51**(1):115-17 doi: 10.1086/653445[published Online First: Epub Date]|.
9. Haubrich RH, Little SJ, Currier JS, et al. The value of patient-reported adherence to antiretroviral therapy in predicting virologic and immunologic response. California Collaborative Treatment Group. AIDS 1999;**13**(9):1099-107
10. Mannheimer S, Friedland G, Matts J, Child C, Chesney M. The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons in clinical trials. Clin Infect Dis 2002;**34**(8):1115-21 doi: CID010623 [pii]

10.1086/339074[published Online First: Epub Date]|.
11. Blaschke TF, Osterberg L, Vrijens B, Urquhart J. Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. Annu Rev Pharmacol Toxicol 2012;**52**:275-301 doi: 10.1146/annurev-pharmtox-011711-113247[published Online First: Epub Date]|.
12. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;**353**(5):487-97 doi: 353/5/487 [pii]

10.1056/NEJMra050100[published Online First: Epub Date]|.
13. WHO. Adherence to long-term therapies: Evidence for action. Secondary Adherence to long-term therapies: Evidence for action 2003. http://www.who.int/chp/knowledge/publications/adherence_report/en/.
14. Logie CH, Lacombe-Duncan A, Wang Y, et al. Pathways From HIV-Related Stigma to Antiretroviral Therapy Measures in the HIV Care Cascade for Women Living With HIV in Canada. JAIDS Journal of Acquired Immune Deficiency Syndromes 2018;**77**(2):144-53 doi: 10.1097/qai.0000000000001589[published Online First: Epub Date]|.
15. Hodgson I, Plummer ML, Konopka SN, et al. A systematic review of individual and contextual factors affecting ART initiation, adherence, and retention for HIV-infected pregnant and postpartum women. PLoS One 2014;**9**(11):e111421 doi: 10.1371/journal.pone.0111421[published Online First: Epub Date]|.
16. Katz IT, Ryu AE, Onuegbu AG, et al. Impact of HIV-related stigma on treatment adherence: systematic review and meta-synthesis. J Int AIDS Soc 2013;**16**(3 Suppl 2):18640 doi: 10.7448/ias.16.3.18640[published Online First: Epub Date]|.
17. Mugavero MJ, Westfall AO, Zinski A, et al. Measuring retention in HIV care: the elusive gold standard. J Acquir Immune Defic Syndr 2012;**61**(5):574-80 doi: 10.1097/QAI.0b013e318273762f[published Online First: Epub Date]|.
18. Geng EH, Nash D, Kambugu A, et al. Retention in Care Among HIV-Infected Patients in Resource-Limited Settings: Emerging Insights and New Directions. Current HIV/AIDS reports 2010;**7**(4):234-44 doi: 10.1007/s11904-010-0061-5[published Online First: Epub Date]|.

19. Rachlis B, Burchell AN, Gardner S, et al. Social determinants of health and retention in HIV care in a clinical cohort in Ontario, Canada. AIDS Care 2017;**29**(7):828-37 doi: 10.1080/09540121.2016.1271389[published Online First: Epub Date]|.
20. Joseph B, Kerr T, Puskas CM, Montaner J, Wood E, Milloy MJ. Factors linked to transitions in adherence to antiretroviral therapy among HIV-infected illicit drug users in a Canadian setting. AIDS Care 2015;**27**(9):1128-36 doi: 10.1080/09540121.2015.1032205[published Online First: Epub Date]|.
21. Kerr T, Palepu A, Barness G, et al. Psychosocial determinants of adherence to highly active antiretroviral therapy among injection drug users in Vancouver. Antivir Ther 2004;**9**(3):407-14
22. Tapp C, Milloy M-J, Kerr T, et al. Female gender predicts lower access and adherence to antiretroviral therapy in a setting of free healthcare. BMC Infectious Diseases 2011;**11**(1):1-7 doi: 10.1186/1471-2334-11-86[published Online First: Epub Date]|.
23. Lourenco L, Nohpal A, Shopin D, et al. Non-HIV-related health care utilization, demographic, clinical and laboratory factors associated with time to initial retention in HIV care among HIV-positive individuals linked to HIV care. HIV Med 2016;**17**(4):269-79 doi: 10.1111/hiv.12297[published Online First: Epub Date]|.
24. Mbuagbaw L, Thabane L, Ongolo-Zogo P, et al. Trends and determining factors associated with adherence to antiretroviral therapy (ART) in Cameroon: a systematic review and analysis of the CAMPS trial. AIDS Research and Therapy 2012;**9**:37-37 doi: 10.1186/1742-6405-9-37[published Online First: Epub Date]|.
25. Skarbinski J, Rosenberg E, Paz-Bailey G, et al. Human immunodeficiency virus transmission at each step of the care continuum in the United States. JAMA internal medicine 2015;**175**(4):588-96 doi: 10.1001/jamainternmed.2014.8180[published Online First: Epub Date]|.
26. Shah M, Risher K, Berry SA, Dowdy DW. The Epidemiologic and Economic Impact of Improving HIV Testing, Linkage, and Retention in Care in the United States. Clin Infect Dis 2016;**62**(2):220-9 doi: 10.1093/cid/civ801[published Online First: Epub Date]|.
27. Mbuagbaw L, Sivaramalingam B, Navarro T, et al. Interventions for Enhancing Adherence to Antiretroviral Therapy (ART): A Systematic Review of High Quality Studies. AIDS Patient Care and STDs 2015 doi: 10.1089/apc.2014.0308[published Online First: Epub Date]|.
28. Barker PM, Reid A, Schall MW. A framework for scaling up health interventions: lessons from large-scale improvement initiatives in Africa. Implement Sci 2016;**11**:12 doi: 10.1186/s13012-016-0374-x[published Online First: Epub Date]|.
29. Willis CD, Riley BL, Stockton L, et al. Scaling up complex interventions: insights from a realist synthesis. Health Res Policy Syst 2016;**14**(1):88 doi: 10.1186/s12961-016-0158-4[published Online First: Epub Date]|.
30. Mathes T, Pieper D, Antoine SL, Eikermann M. Adherence-enhancing interventions for highly active antiretroviral therapy in HIV-infected patients - a systematic review. HIV Med 2013;**14**(10):583-95 doi: 10.1111/hiv.12051[published Online First: Epub Date]|.
31. Charania MR, Marshall KJ, Lyles CM, et al. Identification of Evidence-Based Interventions for Promoting HIV Medication Adherence: Findings from a Systematic Review of U.S.-Based Studies, 1996-2011. AIDS Behav 2013 doi: 10.1007/s10461-013-0594-x[published Online First: Epub Date]|.

32. Higa DH, Crepaz N, Mullins MM. Identifying Best Practices for Increasing Linkage to, Retention, and Re-engagement in HIV Medical Care: Findings from a Systematic Review, 1996–2014. AIDS and Behavior 2016;**20**(5):951-66 doi: 10.1007/s10461-015-1204-x[published Online First: Epub Date]|.
33. Heard A, Peterson K, Modi S, Esper H, Calvo F, Brown AN. Integrating HIV services with other health services to improve care, retention and adherence. 3ie Scoping Report 7. New Delhi: International Initiative for Impact Evaluation (3ie), 2017.
34. Silva V, Grande AJ, Carvalho APVd, Martimbianco ALC, Riera R. Overview of systematic reviews - a new type of study. Part II. Sao Paulo Medical Journal 2015;**133**:206-17
35. Becker LA, Oxman AD. Overviews of reviews. Cochrane handbook for systematic reviews of interventions: Cochrane book series 2008:607-31
36. Palmisano L, Vella S. A brief history of antiretroviral therapy of HIV infection: success and challenges. Annali dell'Istituto superiore di sanitÃ 2011;**47**(1):44-48
37. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;**75**:40-6 doi: 10.1016/j.jclinepi.2016.01.021[published Online First: Epub Date]|.
38. Reuters T. EndNote X7. Thomson Reuters: Philadelphia, PA, USA 2013
39. Bank W. World Bank Open Data. Secondary World Bank Open Data 2018. https://data.worldbank.org/.
40. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. Fam Med 2005;**37**(5):360-3
41. Whiting P, Savovic J, Higgins JP, et al. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol 2016;**69**:225-34 doi: 10.1016/j.jclinepi.2015.06.005[published Online First: Epub Date]|.
42. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;**8**(5):336-41 doi: 10.1016/j.ijsu.2010.02.007[published Online First: Epub Date]|.
43. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;**64**(4):383-94 doi: 10.1016/j.jclinepi.2010.04.026[published Online First: Epub Date]|.
44. Wieland LS, Berman BM, Altman DG, et al. Rating of Included Trials on the Efficacy-Effectiveness Spectrum: development of a new tool for systematic reviews. J Clin Epidemiol 2017;**84**:95-104 doi: 10.1016/j.jclinepi.2017.01.010[published Online First: Epub Date]|.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	N/A
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1,2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	14
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	14
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5, 6, 7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	10
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	10, 11
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	11

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11, 12
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	12
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	12
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	11, 12
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	12
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	13
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	12, 13
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	N/A
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	13
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	N/A
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	13

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.