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# 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

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

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**Key words:**

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**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 (Excerpta 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.

For peer review only

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3 **Article Summary:**

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6 **Article focus**

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- 10 • An outline of the procedures for an overview of systematic reviews of interventions
  - 11 to improve adherence to antiretroviral therapy and retention in care in high income
  - 12 countries
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17 **Key message**

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- 20 • An overview of systematic reviews can provide insight into the most appropriate
- 21 interventions to enhance adherence to medication and retention in care among
- 22 people living with HIV in high income countries
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27 **Strengths and limitations**

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- 30 • An exhaustive and comprehensive search strategy
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- 32 • Findings will be interpreted in light of levels of pragmatism of interventions and
- 33 quality of evidence
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- 37 • Trials not included in systematic reviews will not be evaluated
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## 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 lifetime 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 (Excerpta Medica Database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), PsycINFO, Web of Science and the Cochrane Library. These databases 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 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, 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.

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**Competing interests statement:**

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## 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

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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

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**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 (Excerpta 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 lifetime 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?

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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 (Excerpta Medica Database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), PsycINFO, Web of Science and the Cochrane Library. These databases 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 nonadherence\* 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.

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**Competing interests statement:**

The authors declare none.

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**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
<b>ADMINISTRATIVE INFORMATION</b>			
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
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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 $\tau$ )	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.**

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# 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

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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

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**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 (Excerpta 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 lifetime 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?

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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 (Excerpta Medica Database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), PsycINFO, Web of Science and the Cochrane Library. These databases 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 nonadherence\* 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.

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**Competing interests statement:**

The authors declare none.

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**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
<b>ADMINISTRATIVE INFORMATION</b>			
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
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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 $\tau$ )	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.**

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