Compendium of Evidence-Based Interventions and Best Practices for HIV Prevention:

Background, Methods, and Criteria

PREVENTION RESEARCH SYNTHESIS (PRS) PROJECT

Division of HIV Prevention

Centers for Disease Control and Prevention

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PREVENTION RESEARCH SYNTHESIS

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BACKGROUND

Initiated in 1996, the CDC's HIV Prevention Research Synthesis (PRS) Project systematically reviews and summarizes the cumulative body of HIV-prevention literature to identify Evidence-Based Interventions (EBIs), best practices and public health strategies for reducing HIV transmission and infection. Each eligible study is evaluated against *a priori* criteria to assess the risk of bias and strength of findings. The first PRS efficacy review was for Risk Reduction (CDC 1999) and was based on the original criteria used for the *Compendium of HIV Prevention Interventions with Evidence of Effectiveness*.

The *Compendium of Evidence-Based Interventions and Best Practices for HIV Prevention* is a collection of HIV interventions in the form of individual study information summary PDFs. Starting in January of 2024, PDFs were phased out as a mechanism of CDC's Clean Slate website initiative. All interventions are now listed in the Compendium Search (PDFs are linked if available).

The *Compendium* includes five chapters [year established]:

- Risk Reduction (RR) [1996]
- Medication Adherence (MA) [2010]
- Linkage to, Retention in, and Re-engagement in HIV Care (LRC) [2013]
- Structural Interventions (SI) [2017]
- Pre-Exposure Prophylaxis (PrEP) [2020]

Each intervention study is evaluated according to specific chapter criteria and assigned a level of evidence. The evaluation is then translated into an intervention summary that is categorized as an Evidence-Based Intervention (EBI) or Evidence-Informed Intervention (EI). EBIs provide the strongest evidence of efficacy. EIs have some evidence of working and ideally, need further testing with a comparison group or with larger samples.

Evidence-Based Interventions

- Shown to have significant effects in HIV-related outcomes
- Tested with a comparison group
- EBIs work, are rigorously evaluated and provide the strongest evidence of efficacy

Evidence-Informed Interventions

- Shown to have significant effects in HIV-related outcomes
- Tested with a weaker design or fewer participants
- EIs have some evidence of working and need further testing

See methodology and criteria for all chapters below.

For a history of the PRS Project's work in research synthesis, including systematic reviews and meta-analyses, please see the narrative review published in 2022 in Public Health Reports.

METHODS

The process for identifying interventions is conducted using systematic procedures for searching and reviewing the research literature. Comprehensive search strategies, using automated and manual techniques, were developed, tested, and implemented by experienced librarians to locate published and unpublished citations to build the PRS Project database (1988 – present). The searches use automated and manual search methods to decrease the chance of missing pertinent information.

The database is updated annually in five research areas:

- HIV, AIDS, or STD behavioral prevention interventions
- Linkage to, retention in, engagement in, and re-engagement in HIV care interventions
- HIV, AIDS, antiretroviral therapy (ART) treatment and adherence interventions
- HIV, AIDS, or STD and pre-exposure prophylaxis (PrEP) interventions
- Systematic reviews on HIV and AIDS

Automated searches use the following electronic bibliographic databases to retrieve published literature: CAB Global Health, CINAHL, EMBASE, MEDLINE, PsycINFO, and Sociological Abstracts. These searches are tested and enhanced each year. A detailed overview of the database search strategy is available in the article *Developing a Comprehensive Search Strategy for Evidence Based Systematic Reviews* in the journal *Evidence Based Library and Information Practice*.

The manual search consists of reviewing journals (see below) to identify articles not yet indexed in the electronic databases. As of November 2023, the journal list totals 20 titles. The hand search list of journals is changed to reflect recent publishing trends. The list of journals may change on a year-to-year basis. Quarterly, team members screen all issues of the journals published within the 3 previous months to locate relevant articles. In addition, reference lists of published articles, HIV/AIDS Internet listservs, and unpublished manuscripts submitted by study authors are examined for related materials.

Manual search journal List

AIDS
AIDS and Behavior
AIDS Care
AIDS Education and Prevention
AIDS Patient Care and STDs
American Journal of Public Health
BMC Infectious Diseases
BMJ Open
Clinical Infectious Diseases
HIV Medicine
International Journal of STD & AIDS
JAIDS J of Acq Immune Deficiency Syndromes
JMIR mHealth & uHealth
Journal of the Assoc of Nurses in AIDS Care
Journal of the International AIDS Society
Lancet HIV
Open Forum Infectious Diseases
PLoS Medicine
PLoS ONE
Sexually Transmitted Diseases

Risk Reduction (RR) Efficacy Criteria

The RR Chapter was the first efficacy review to be developed by the PRS project in 1996. RR Efficacy Criteria identifies EBIs that show evidence of efficacy in changing sex or drug-injection behaviors that impact HIV-transmission risk. There are many ways to reduce the risk of acquiring or transmitting HIV:

- Using medicines to treat HIV
- Using medicines to prevent acquisition of HIV
- Reducing sex and drug risk behaviors (e.g., condom use, clean needle use, testing for HIV or STIs)

Starting in 2015, PRS narrowed its focus to evaluate only interventions for priority populations:

- People with HIV (PWH)
- Men who have sex with men (MSM)
- Transgender persons
- People who use drugs (PWUD)
- Black or African American women (2022)
- Youth (2023)

These priority populations are determined by the CDC. Interventions that are more than 10 years old and focus on a non-priority population are archived. Archived Interventions are marked as such.

Because most community-level interventions (CLIs) have study and design features that cannot be evaluated with the criteria for ILIs/GLIs/CPLs, PRS developed criteria for finding evidence-based CLIs in 2008. These criteria were developed in consultation with methodologists and HIV prevention researchers. CLI efficacy criteria focus on quality of study design, quality of study implementation or analysis, and strength of evidence. CLI EBIs are also classified as either best- or good-evidence.

Evidence-Based Interventions BEST EVIDENCE	**Evidence-Based Interventions GOOD EVIDENCE**
• Clear description of key aspects • Prospective study design • Appropriate and concurrent comparison arm • Random or minimally biased assignment to study arms • Shown to have significant and positive evidence of efficacy. These interventions are scientifically rigorous and provide the **strongest evidence** of efficacy.	• Clear description of key aspects • Prospective or quasi-prospective study design • Appropriate/concurrent comparison arm or historical comparison • Random, minimally biased, or moderately biased allocation to study arms • Shown to have significant and positive evidence of efficacy These interventions are scientifically sound and provide **sufficient evidence** of efficacy.

Criteria for RR Best-Evidence Individual-Level, Group-Level, and Couple-Level Interventions (ILIs/GLIs/CPLs)

Intervention Description

- Clear description of key aspects of the intervention

Quality of Study Design

- Prospective study design
- Appropriate and concurrent comparison arm
- Random or minimally biased assignment of subjects to study arms

Quality of Study Implementation and Analysis

- Follow-up assessment ≥ 3-months post completion of intervention for each study arm with recall not referring to pre-intervention period (except for HIV testing outcomes)
- At least a 70% retention rate at a single follow-up assessment for each study arm
- Comparison between intervention arm and an appropriate comparison arm
- Analysis of participants in study arms as originally allocated regardless of contamination or logistic/implementation issues
- Analysis of participants regardless of the level of intervention exposure
- Use of appropriate cluster-level analyses if assigned to study arms by cluster or group
- Analysis must be based on post-intervention levels or on pre-post changes in measures
    - For pre-post changes used in analysis, measures must be identical, including identical recall period
- Analysis based on an $\alpha = .05$ (or more stringent) and a 2-sided test
- With nonrandomized assignment, either no statistical differences in baseline levels of the outcome exist or baseline differences are controlled for in the analysis
- Analytic sample ≥ 50 participants per study arm

Strength of Evidence

Demonstrated Significant Positive Intervention Effects

- Positive and statistically significant ($p < .05$) intervention effect for ≥1 relevant outcome measure
- A positive intervention effect is defined as a greater reduction in HIV/STD incidence or risk behaviors or a greater increase in HIV protective behaviors in the intervention arm relative to the comparison arm
- A relevant outcome is defined as a behavior (e.g., abstinence, mutual monogamy, number of sex partners, consistent condom use with anal/vaginal sex, unprotected anal/vaginal sex, proportion of anal/vaginal sex acts protected, injection drug use, sharing or borrowing needles/works) - that directly impacts HIV risk, a biologic measure indicating HIV or STD infection (i.e., HIV or STD incidence) or HIV testing (if HIV test results are reported)
- Effect at the follow-up and based on the analyses that meet study implementation and analysis criteria

No Demonstrated Significant Negative Intervention Effects

- No negative and statistically significant ($p < .05$) intervention effect for any relevant outcome

- A negative intervention effect is defined as a greater increase in HIV/STD incidence or risk behaviors or a greater decrease in HIV protective behaviors in the intervention arm relative to the comparison arm.
- No other statistically significant harmful intervention effect
- For an intervention with a replication evaluation, no significant negative intervention effects in the replication study

Additional Limitations to Evaluate

- No evidence that additional limitations resulted in a fatal flaw:
    - A fatal flaw has occurred when the overall evaluation of limitations indicates they resulted in considerable bias, thus substantially reducing the confidence of the findings.
    - Examples of item limitations to check for possible fatal flaw:
        - Effects only found within a potentially biased subset analysis;
        - Substantial missing data. Missing data plus loss to attrition exceeds acceptable limits for retention alone (≥ 40%)
        - Study arm non-equivalence: statistically significant differences between arms in important baseline demographics or risk factors not controlled-for in analysis
        - Differential retention: (1) significant difference between study arms in characteristics among participants retained or lost to follow-up; OR (2) more than minimal rate of differential retention (>10%)
        - Intervention activities did not match with the intervention concepts or guiding theories intended to produce the desired outcomes
        - Did not clearly describe issues related to generalizability
        - Too many post hoc analyses (even with Bonferroni corrections)
        - Inconsistent findings

All criteria must be satisfied for an intervention to be considered as a Best-Evidence Individual-level, Group-level, or Couple-level intervention.

Criteria for RR Good-Evidence Individual-Level, Group-Level, and Couple-Level Interventions (ILIs/GLIs/CPLs)

Intervention Description

- Clear description of key aspects of the intervention

Quality of Study Design

- Prospective or quasi-prospective study design
- Appropriate and concurrent comparison arm, or historical comparison (provided it is similar to the intervention arm with respect to population, setting, and time frame in the epidemic, and identical with respect to follow-up interval, recall period, and outcome measures)
- Random, minimally biased, or moderately biased allocation of participants to study arms, allowing for selection bias unrelated to the intervention or HIV risk. Assignment may be based on pre-established groups or selection into something other than the intervention, provided neither is directly related to HIV risk.

Quality of Study Implementation and Analysis

- Follow-up assessment ≥ 1 month post-completion of intervention for each study arm with recall not referring to pre-intervention period except for HIV testing outcomes
- At least a 60% retention rate (or medical chart recovery) at a single follow-up for each study arm
- Comparison between intervention arm and an appropriate comparison arm
- Analysis of participants in study arms as originally allocated, or contaminated participants may be excluded if numbers are small, but participants may not be re-assigned for analytic purposes
- Analysis of participants may be based on intervention exposure, where participants exposed to < 50% of the entire intended intervention may be excluded
- If participants excluded due to contamination or low exposure (as described above), retention rate must include these participants at each follow-up they were assessed
- Analysis must be based on post-intervention levels or on pre-post changes in measures
    - For pre-post changes used in analysis, measures must be identical, including identical recall period
- Analysis based on an α =.05 and either a 2-sided test or 1-sided test if an *a priori* direction is hypothesized
- With nonrandomized assignment, either no statistical differences exist in baseline levels of the outcome measure, or baseline differences must be controlled for in the analysis. If moderately biased assignment or historical comparison was used, differences in baseline demographics also must be controlled for in the analysis.
- Analytic sample of ≥ 40 participants per study arm

Strength of Evidence

Demonstrated Significant Positive Intervention Effects

- Positive and statistically significant ($p < .05$) intervention effect for ≥ 1 relevant outcome measure
- A positive intervention effect is defined as a greater reduction in HIV/STD incidence or risk behaviors or a greater increase in HIV protective behaviors in the intervention arm relative to the comparison arm
- A relevant outcome is defined as a behavior (e.g., abstinence, mutual monogamy, number of sex partners, consistent condom use with anal/vaginal sex, unprotected anal/vaginal sex, proportion of anal/vaginal sex acts protected, injection drug use, sharing or borrowing needles/works) that directly impacts HIV risk, a biologic measure indicating HIV or STD infection (i.e., HIV or STD incidence) or HIV testing (if HIV test results are reported)
- Effect at the follow-up and based on the analyses that meet study implementation and analysis criteria

No Demonstrated Significant Negative Intervention Effects

- No negative and statistically significant ($p < .05$) intervention effect for any relevant outcome
- A negative intervention effect is defined as a greater increase in HIV/STD incidence or risk behaviors or a greater decrease in HIV protective behaviors in the intervention arm relative to the comparison arm.
- No other statistically significant harmful intervention effect
- For an intervention with a replication evaluation, no significant negative intervention effects in the replication study

Additional Limitations to Evaluate

- No evidence that additional limitations resulted in a fatal flaw:
  - A fatal flaw has occurred when the overall evaluation of limitations indicates they resulted in considerable bias, thus substantially reducing the confidence of the findings.
  - Examples of item limitations to check for possible fatal flaw:
    - Effects only found within potentially biased subset analyses
    - Substantial missing data: Missing data plus loss to attrition exceeds acceptable limits for retention alone (≥ 40%)
    - Study arm non-equivalence: statistically significant differences between arms in important baseline demographics or risk factors not controlled for in analyses
    - Differential Retention: (1) significant difference between study arms in characteristics among participants retained or lost to follow-up; OR (2) more than minimal rate of differential retention (> 10%)
    - Intervention activities did not match with the intervention concepts or guiding theories intended to produce the desired outcomes
    - Did not clearly describe issues related to generalizability
    - Too many post hoc analyses (even with Bonferroni corrections)
    - Inconsistent findings

All criteria must be satisfied for an intervention to be considered as a Good-Evidence Individual-level, Group-level, or Couple-level intervention.

Source for Best and Good ILIs/GLIs/CPL interventions: Lyles et al., (2006) and Lyles at al., (2007)

Criteria for RR Best-Evidence Community-Level Interventions

Intervention Description

- Clear description of key aspects of the intervention

Quality of Study Design

- Prospective study design
- Appropriate and concurrent control/comparison arm
- ≥ 4 communities per arm or appropriate power analysis indicating that a smaller number of communities was adequate (i.e., 2 or 3 communities per arm)
- Select similar communities (units) for assignment
  - To minimize selection bias before assignment regardless of assignment methods (randomization or not); use methods such as systematic, *a priori* approaches to choose intervention and control communities that are similar (e.g., matching or stratification on factors related to important/appropriate community characteristics)

Quality of Study Implementation and Analysis

- Sample individuals from assigned communities in acceptable ways (e.g., random, systematic) and use identical methods and eligibility criteria for selecting participants in each community, study arm, and data collection wave

    - If demographic differences are identified *a priori*, differential selection (e.g., over-sampling based on demographics) may be used to achieve equivalence between study arms on those factors
- Follow-up assessment ≥ 3 months post completion of entire time specific CLI or post full implementation of on-going CLI with recall not referring to pre-intervention period
    - "Post full implementation of an on-going CLI" means after all components of the CLI have been started or put in place in communities
- If cohort, at least 70% retention rate at a single follow-up assessment for each study arm
    - If cohort chart review, ≥ 70% success rate in matching medical records
- Comparison between intervention arm and an appropriate comparison arm
- Analysis of communities (units) and analysis of individuals within the communities as originally assigned regardless of contamination or logistic/implementation issues
- Analysis of communities (units) regardless of community level of intervention exposure
- Analysis of individuals within the communities (units) regardless of individual level of intervention exposure
- Use of appropriate cluster-level analyses, e.g., adjusting for ICC
- Analysis must be based on post-intervention levels or among pre-post changes in measures
    - For pre-post changes used in analysis, measures must be identical, including identical recall period
- Analysis based on an $\alpha = .05$ (or more stringent) and a 2-sided test
- Either no statistical differences in baseline levels of the outcome exist or baseline differences are controlled for in the analysis, regardless of allocation method (e.g., randomization, non-randomization)
    - No differences on baseline levels of the outcome means reporting no significant difference between groups on BL relevant outcomes or match/stratify/statistically adjust participant data by using propensity scores or relevant outcome covariates (regardless of assignment methods - RCT or non-RCT)

Strength of Evidence

Demonstrated Significant Positive Intervention Effects

- Positive and statistically significant ($p < .05$) intervention effect for ≥ 1 relevant outcome measure
    - A positive intervention effect is defined as a greater reduction in HIV/STD incidence or risk behaviors or a greater increase in HIV protective behaviors in the intervention arm relative to the comparison arm
    - A relevant outcome is defined as a behavior (e.g., abstinence, mutual monogamy, number of sex partners, consistent condom use with anal/vaginal sex, unprotected anal/vaginal sex, proportion of anal/vaginal sex acts protected, injection drug use, sharing or borrowing needles/works) that directly impacts HIV risk, a biologic measure indicating HIV or STD infection (i.e., HIV or STD incidence) or HIV testing (if HIV test results are reported)
- Effect at the follow-up and based on the analyses that meet study implementation and analysis criteria

No Demonstrated Significant Negative Intervention Effects

- No negative and statistically significant ($p < .05$) intervention effect for any relevant outcome

- A negative intervention effect is defined as a greater increase in HIV/STD incidence or risk behaviors or a greater decrease in HIV protective behaviors in the intervention arm relative to the comparison arm
- No other statistically significant harmful intervention effect
- For an intervention with a replication evaluation, no significant negative intervention effects in the replication study

Additional Limitations to Evaluate

- No evidence that additional limitations resulted in a fatal flaw:
  - A fatal flaw has occurred when the overall evaluation of limitations resulted in considerable bias, thus substantially reducing the confidence of the findings
  - Examples of limitations to check for possible fatal flaw:
    - Group non-equivalence in baseline measures of important demographics or risk factors
    - Differential Retention (for cohort studies): (1) association between study arms and characteristics related to retention or attrition; OR (2) more than minimal rate of differential retention (> 10%)
    - Differential Refusal: At baseline for cohort studies; by wave for serial cross-sectional studies: (1) association between study arms and characteristics related to refusal; OR (2) more than minimal rate of differential refusal rate (> 100)
    - Intervention activities did not match with the intervention concepts or guiding theories intended to produce the desired outcomes
    - Did not clearly describe issues related to generalizability
    - Effects only found within a potentially biased subset analysis
    - Substantial missing data (> 10% or missing data plus loss to attrition does not exceed acceptable limits for retention alone)
    - Too many post hoc analyses (even with Bonferroni corrections)
    - Pilot study or very small sample size per study arm (< 50)

Criteria for RR Good-Evidence Community-Level Interventions

Intervention Description

- Clear description of key aspects of the intervention

Quality of Study Design

- Prospective or quasi-prospective study design
- Appropriate and concurrent comparison arm, or historical comparison (provided it is similar to intervention arm with respect to population, setting, time frame in the epidemic, and identical with respect to follow-up time, recall period, and outcome measures)
- Post hoc selection of comparison is allowed
- ≥ 1 community per arm
- 1 community per arm is acceptable only if the following conditions are met: (1) there is a significant pre- and post-intervention change in the relevant outcome for the intervention arm, and (2) the significant pre- and post-intervention change is based on appropriate participant-level analysis or repeated-measures analysis
- Select similar communities (units) for assignment

- To minimize selection bias before assignment regardless of random assignment or other assignment methods, used methods such as systematic, *a priori* approaches to select intervention and comparison communities that are similar (e.g., matching or stratification on factors related to important/appropriate community characteristics)

Quality of Study Implementation and Analysis

- Sample individuals from assigned communities in acceptable ways (e.g., random, systematic) and use identical methods and eligibility criteria for selecting participants in each community, study arm, and data collection wave
    - If demographic differences are identified *a priori*, differential selection (e.g., over-sampling based on demographics) may be used to achieve equivalence between study arms on those factors
- Follow-up assessment ≥ 1-month post completion of entire time-specific CLI or post full implementation of on-going CLI with recall not referring to pre-intervention period except for HIV testing outcomes
    - "Post full implementation of on-going CLI" means after all components of the CLI have been started or put in place in communities
- If cohort, at least 60% retention rate (or medical chart recovery) at a single follow-up assessment for each study arm
- Comparison between intervention arm and an appropriate comparison arm
- Analysis of communities (units) as originally assigned, or communities may be excluded due to contamination or logistic/implementation issues only if dropping no more than one community per study arm AND retaining at least two thirds of intended communities
- Analysis of individuals within the communities (units) as originally assigned, or contaminated individuals may be excluded if numbers are small, but individuals may not be reassigned for analytic purposes
- Analysis of communities (units) regardless of community level of intervention exposure
- Analysis of individuals within the communities (units) may be based on intervention exposure, where dropping individuals who were not exposed to any intervention component (e.g., have not heard of or recognized intervention materials) would retain at least 60% of total sample
- Cluster-level analyses may be provided, but is not required
- Analysis must be based on post-intervention levels or among pre-post changes in measures
    - For pre-post changes used in analysis, measures must be identical, including identical recall period
- Analysis based on an $\alpha = .05$ and either a 2-sided test or 1-sided test if an *a priori* direction is hypothesized
- Either no statistical differences in baseline levels of the outcome exist or baseline differences are controlled for in the analysis, regardless of allocation method (e.g., randomization, non-randomization)
- No differences on baseline levels of the outcome means reporting no significant difference between study arms in baseline relevant outcome measures, or match/stratify/statistically adjust participant data by using propensity scores or relevant outcome covariates (regardless of assignment methods – RCT or non-RCT)

Strength of Evidence

Demonstrated Significant Positive Intervention Effects

- Positive and statistically significant ($p < .05$) intervention effect for ≥ 1 relevant outcome measure
  - A positive intervention effect is defined as a greater reduction in HIV/STD incidence or risk behaviors or a greater increase in HIV protective behaviors in the intervention arm relative to the comparison arm
  - A relevant outcome is defined as a behavior (e.g., abstinence, mutual monogamy, number of sex partners, consistent condom use with anal/vaginal sex, unprotected anal/vaginal sex, proportion of anal/vaginal sex acts protected, injection drug use, sharing or borrowing needles/works) that directly impacts HIV risk, a biologic measure indicating HIV or STD infection (i.e., HIV or STD incidence) or HIV testing (if HIV test results are reported)
- Effect at the follow-up and based on the analyses that meet study implementation and analysis criteria

No Demonstrated Significant Negative Intervention Effects

- No negative and statistically significant ($p < .05$) intervention effect for any relevant outcome
  - A negative intervention effect is defined as a greater increase in HIV/STD incidence or risk behaviors or a greater decrease in HIV protective behaviors in the intervention arm relative to the comparison arm
- No other statistically significant harmful intervention effect
- For an intervention with a replication evaluation, no significant negative intervention effects in the replication study

Additional Limitations to Evaluate

- No evidence that additional limitations resulted in a fatal flaw:
  - A fatal flaw has occurred when the overall evaluation of limitations indicate they resulted in considerable bias, thus substantially reducing the confidence of the findings
  - Examples of limitations to check for possible fatal flaw:
    - Study arm non-equivalence: statistically significant differences between arms in important baseline demographics or risk factors
    - Differential Retention (for cohort studies): (1) association between study arms and characteristics related to retention or attrition; OR (2) more than minimal rate of differential retention (> 10%)
    - Differential Refusal – at baseline for cohort studies; by wave for serial cross-sectional studies: (1) association between study arms and characteristics related to refusal; OR (2) more than minimal rate of differential refusal rate (> 10%)
    - Intervention activities did not match with the intervention concepts or guiding theories intended to produce the desired outcomes
    - Did not clearly describe issues related to generalizability
    - Effects only found within potentially biased subset analyses
    - Substantial missing data (> 10%, or missing data plus loss to attrition exceeds acceptable limits for retention alone)
    - Too many post hoc analyses (even with Bonferroni corrections)
    - Pilot study or very small sample size per study arm (< 40)
    - Inconsistent finding

Medication Adherence (MA) Efficacy Criteria

The MA Chapter identifies EBIs for improving HIV medication adherence and viral load suppression among persons with HIV (PWH). Due to the availability and advancement of antiretroviral therapy, as well as an increasing number of persons with HIV, there has been an increased focus on both health promotion and HIV prevention for PWH. Optimal adherence to ART is critical to fully achieve both the clinical and preventive benefits of ART. These criteria were developed between 2008 and 2010. Criteria last updated October 26, 2020.

Evidence-Based Interventions BEST EVIDENCE	**Evidence-Based Interventions GOOD EVIDENCE**
• Clear description of key aspects • Prospective study design • Appropriate and concurrent comparison arm • Random allocation to study arms **Best-evidence** HIV medication adherence interventions for persons with HIV: • Show significant effects in improving medication adherence behaviors **AND** • Show significant effects in reducing HIV viral load These interventions are rigorously evaluated and provide the strongest evidence of efficacy.	• Clear description of key aspects • At least a quasi-prospective study design • Appropriate or non-concurrent comparison arm • At least a non-random allocation **Good-evidence** HIV medication adherence interventions for persons with HIV: • Show significant effects in improving medication adherence **OR** • Show significant effects in reducing HIV viral load These interventions are scientifically sound and provide sufficient evidence of efficacy.

Criteria for MA Best-Evidence Interventions

Intervention Description

- Clear description of key aspects of the intervention

Quality of Study Design

- Prospective study design
- Appropriate comparison arm
- Concurrent comparison arm
- Random or minimally biased assignment of subjects to study arms

Quality of Study Implementation

- At least a 3-month post-intervention follow-up assessment for each study arm (with recall referring to post-intervention period only) for interventions that are clearly discrete or at least a 6-month post-initiation follow-up assessment for each study arm for all other types of interventions
- At least a 70% retention rate (or medical chart recovery) at all assessment time points for each study arm

Quality of Study Analysis

- Analysis contrasting intervention arm and an appropriate comparison arm
- Intent-to-treat analysis:
  - Analysis of participants in study arms as originally allocated
  - Analysis of participants regardless of the level of intervention exposure
  - Analysis using appropriate imputations to account for missing data due to attrition or other reasons
- Use of appropriate cluster-level analyses if allocated to study arms by cluster
- Comparability of measures:
  - Measures must be identical, including recall, for any repeated measures or change score analyses
  - Baseline measures do not have to be identical, but must be of the same construct as outcome measures, if being used as a covariate in analyses (i.e., adjusted for BL)
- Analysis based on a 2-sided test and an $\alpha = .05$ (or more stringent)
- Analytic sample of at least 50 participants per study arm

Strength of Evidence

Demonstrated Significant Positive Intervention Effects

- Positive and statistically significant ($p < .05$) intervention effect for at least 1 relevant behavioral outcome measure and 1 relevant biologic outcome measure
  - A positive intervention effect is defined as a statistically significant greater improvement in, or better level of, medication adherence behavioral or biologic outcome in the intervention arm relative to the comparison arm
  - A relevant behavioral outcome measure may include electronic data monitoring (e.g., MEMs caps), pill count, pharmacy refill, or self-reported adherence. A relevant biologic outcome measure may include a lab test or medical chart recovery of HIV viral load levels
- Effect at the follow-up and based on the analyses that meet study design, implementation and analysis criteria

No Demonstrated Negative Intervention Effects

- No negative and statistically significant ($p < .05$) intervention effect for any HIV-related behavioral or biologic outcome
  - A negative intervention effect is defined as a statistically significant greater improvement in, or better level of, HIV-related behavioral or biologic outcomes in the comparison arm relative to the intervention arm.
- No other statistically significant harmful intervention effect
- For an intervention with an evaluation of a replication, no significant negative intervention effects in the replication study

Additional Limitations to Evaluate

- The totality of the limitations (as described below) cannot introduce considerable bias that substantially reduces the confidence placed on the findings.
- Examples of limitations include:
  - Intervention and comparison arms did not receive similar medication regimens
  - Findings based on too many post-hoc analyses
  - Inconsistent evidence between effects
  - Inconsistent evidence across intervention comparisons within the study
  - Effects only found within a potentially biased subgroup analysis
  - Substantial (>40%) overall missing data (due to attrition and non-attrition such as missing responses)
  - Substantial differential attrition in rates (>10%) or participant characteristics across study arms
  - Differences in characteristics between those lost-to-follow up and those retained in the study
  - Any other notable bias threatening internal or external validity

All criteria must be satisfied for an intervention to be considered as a Best-Evidence MA intervention.

Criteria for MA Good-Evidence Interventions

Intervention Description

- Clear description of key aspects of the intervention

Quality of Study Design

- At least a quasi-prospective study design
- Appropriate comparison arm
- At least a non-concurrent comparison arm that was implemented within 12 months of the start of the intervention and was similar with respect to population characteristics and setting
- At least non-random allocation with moderate selection bias unrelated to the intervention or adherence behavior

Quality of Study Implementation

- At least a 1-month post-intervention follow-up assessment for each study arm (with recall referring to post-intervention period only) for interventions that are clearly discrete or at least a 3-month post-initiation follow-up assessment for each study arm for all other types of interventions
- At least a 60% retention rate (or medical chart recovery) at all assessment time points for each study arm

Quality of Study Analysis

- Analysis contrasting intervention arm and an appropriate comparison arm
- Intent-to-treat analysis:
  - Analysis of participants in study arms as originally allocated
  - Analysis of participants regardless of the level of intervention exposure
- Comparability of measures:

    - Measures must be identical, including recall, for any repeated measures or change score analyses
    - Baseline measures do not have to be identical, but must be of the same construct as outcome measures, if being used as a covariate in analyses (i.e., adjusted for BL)
- Analysis based on a 2-sided test and an α =.05 (or more stringent)
- Analytic sample of at least 40 participants per study arm
- Non-randomized controlled trials (non-RCTs) must either demonstrate baseline equivalence or control for baseline differences in outcome variables. Non-RCTs with moderate bias must also demonstrate baseline equivalence or control for baseline differences in demographics and other critical variables.

Strength of Evidence

Demonstrated Significant Positive Intervention Effects

- Positive and statistically significant ($p < .05$) intervention effect for at least 1 relevant behavioral outcome measure or 1 relevant biologic outcome measure
- A positive intervention effect is defined as a statistically significant greater improvement in, or better level of, medication adherence behavioral or biologic outcome in the intervention arm relative to the comparison arm
- A relevant behavioral outcome measure may include electronic data monitoring (e.g., MEMs caps), pill count, pharmacy refill, or self-reported adherence. A relevant biologic outcome measure may include a lab test or medical chart recovery of HIV viral load levels
- Effect at the follow-up and based on the analyses that meet study design, implementation and analysis criteria

No Demonstrated Negative Intervention Effects

- No negative and statistically significant ($p < .05$) intervention effect for any HIV-related behavioral or biologic outcome
    - A negative intervention effect is defined as a statistically significant greater improvement in, or better level of, HIV-related behavioral or biologic outcomes in the comparison arm relative to the intervention arm
- No other statistically significant harmful intervention effect
- For an intervention with a replication evaluation, no significant negative intervention effects in the replication study

Additional Limitations to Evaluate

- The totality of the limitations (as described below) cannot introduce considerable bias that substantially reduces the confidence placed on the findings.
- Examples of limitations include:
    - Intervention and comparison arms did not receive similar medication regimens
    - Findings based on too many post-hoc analyses
    - Inconsistent evidence between effects
    - Inconsistent evidence across intervention comparisons within the study
    - Effects only found within a potentially biased subgroup analysis
    - Substantial (>40%) overall missing data (due to attrition and non-attrition such as missing responses)

- Substantial differential attrition in rates (>10%) or participant characteristics across study arms
- Differences in characteristics between those lost-to-follow up and those retained in the study
- Any other notable bias threatening internal or external validity

All criteria must be satisfied for an intervention to be considered as a Good-Evidence MA intervention.

Linkage to, Retention in, and Re-engagement in HIV Care (LRC) Efficacy Criteria

The LRC Chapter identifies best practices for helping persons with HIV engage and remain in HIV care to ensure appropriate treatment and achieve viral suppression. These criteria were finalized in 2013 after a series of consultations with methodologists, HIV prevention researchers, and a key federal partner, the National Institute of Mental Health (NIMH). Criteria last updated April 26, 2023.

Evidence-Based Interventions	Evidence-Informed Interventions
• Evaluate interventions with a comparison arm • Sample size is ≥ 40 per arm • Demonstrate significant positive effects for improving LRC outcomes LRC EBIs provide the **strongest** evidence of efficacy.	• Evaluate interventions that have one-group designs and pre-post data • Evaluate interventions with a comparison arm (sample <40 but ≥ 25 per arm) • Demonstrate significant positive effects for improving LRC outcomes Interventions have **some evidence** of working and ideally, need further testing with a comparison group or with larger samples.

Criteria for LRC Evidence-Based Interventions

Quality of Study design

- Prospective or quasi-prospective study design
- Appropriate and concurrent comparison arm, or appropriate non-concurrent comparison arm that was implemented in a different clinic or agency within 12 months of the start of the intervention and was similar with respect to population and setting
- Random allocation of participants to study arms or if non-randomization, potential bias in allocation to intervention is minimized

Quality of Study implementation and analysis

- For linkage to care interventions, linkage to care occurred within or less than 1 month after the initiation of the intervention
- For retention in care interventions, retention in care occurred at least 6 months after the initiation of the intervention
- Comparison between intervention arm and an appropriate comparison arm
- Analysis of participants in study arms as originally allocated, or contaminated participants may be excluded if numbers are small, but participants may not be re-assigned for analytic purposes

- Analysis of participants may be based on intervention exposure, where participants exposed to < 50% of the entire intended intervention may be excluded
- Analysis must be based on between-group comparisons on post-intervention levels or on pre-post changes in measures
- For pre-post changes used in analysis, measures must be identical, including identical recall period
- Analysis based on a 2-sided test with a p value < 0.05
- With nonrandomized assignment, either no statistical differences exist in baseline levels of the outcome measure, or baseline differences must be controlled for in the analysis. If moderately biased assignment or historical comparison was used, differences in baseline demographics also must be controlled for in the analysis
- Baseline sample of ≥ 40 participants (or charts) per study arm

Strength of Evidence

Demonstrated Significant Positive Intervention Effects

- Statistically significant ($p < 0.05$) positive intervention effect for ≥ 1 relevant outcome measure
    - A positive intervention effect is defined as an improvement in linking to, retention in, engagement in, or re-engagement in HIV medical care, ART initiation, or HIV viral suppression in the intervention arm relative to the comparison arm
    - A relevant outcome is defined as an actual/completed outpatient primary HIV medical care visit or HIV viral load and/ or CD4 count when used as proxies for a HIV medical care visit, or HIV viral suppression
        - Completed HIV medical visits must be documented in medical records, administrative or agency records, or surveillance reports
        - Self-reports of completed medical visits validated by medical records, administrative or agency records are also acceptable:
            - For *linkage to care*, a relevant outcome is the actual/completed first HIV medical visit for persons with a new or recent HIV diagnosis within 1 month
            - For *retention in care*, a relevant outcome is having actual/completed multiple HIV medical visits over a period of time
            - For *engagement in care*, a relevant outcome is at least one actual/completed HIV medical visit
            - For *re-engagement in care*, a relevant outcome is the actual/completed initial HIV medical visit for HIV-positive persons who were out of care, but have returned to HIV care
    - ART initiation is a relevant outcome if there is an improvement in ART initiation in the intervention arm relative to the comparison arm
        - Lab reports, agency records, medical chart abstraction are acceptable
        - Self-report without validation is acceptable
    - HIV viral suppression is a relevant outcome if there is an improvement in viral suppression levels in the intervention arm relative to the comparison arm
        - HIV viral suppression must be measured using a lab report or medical chart abstraction.
    - Effect at a required follow-up assessment time point and based on the analyses that meets all study implementation and analysis criteria

No Demonstrated Significant Negative Intervention Effects

- No statistically significant ($p < 0.05$) negative intervention effect for any relevant outcome
    - A negative intervention effect is defined as a worsening in linkage to, retention in, engagement in or re-engagement in HIV medical care, ART initiation, or HIV viral suppression in the intervention arm relative to the comparison arm
- No other statistically significant harmful intervention effect that causes substantial concern
- For an intervention with a replication evaluation, no significant negative intervention effects in the replication study if the intervention was implemented in the exact same way as the original study and with the same or similar cohort/population

Additional Limitations to Evaluate

- No evidence that additional limitations resulted in considerable bias that reduces the confidence of the findings
    - Examples of limitations:
        - Too many post-hoc analyses
        - Inconsistent evidence between effects
        - Inappropriate subset analyses
        - Not accounting for various reasons why participants were not included in the LRC outcome
        - Not adjusting for cluster effects for studies that allocate individuals to a group-level intervention
        - Not accounting for factors that may influence findings, but are not attributable to the intervention (e.g., historical events)
        - Other notable biases threatening internal or external validity

All criteria must be satisfied for an intervention to be considered an LRC EBI.

Criteria for LRC Evidence-Informed Interventions

Quality of Study design

- Evaluates data before and after intervention implementation in studies without a comparison arm

Quality of Study implementation and analysis

- For pre-post intervention changes, analysis based on a 2-sided test with a p value of < 0.05

Strength of Evidence

Demonstrated Significant Positive Intervention Effects

- Statistically significant ($p < 0.05$) positive pre- to post-intervention effect for ≥ 1 relevant outcome measure
    - A positive intervention effect is defined as an improvement in engaging in, linking to, retention in, or re-engagement in HIV medical care, or viral suppression from pre- to post-intervention
    - A relevant outcome is defined as an actual/completed outpatient primary HIV medical care visit or HIV viral load and/or CD4 counts when used as proxies

        - Completed HIV medical visits must be documented in medical records, administrative or agency records, or surveillance reports
        - Self-reports of completed medical visits validated by medical records, administrative or agency records are also acceptable:
            - For *linkage to care*, a relevant outcome is the actual/completed first HIV medical visit for persons with a new or recent diagnosis of HIV within 1 month
            - For *retention in care*, a relevant outcome is having actual/completed multiple HIV medical visits over a period of time, the minimum being 6 months
            - For *engagement in care*, a relevant outcome is an actual/completed HIV medical visit
            - For *re-engagement in car*e, a relevant outcome is the actual/completed initial HIV medical visit for persons who are HIV positive and were out of care, but have returned to, HIV care
    - ART initiation is a relevant outcome if there is an improvement in ART initiation from pre- to post-intervention
        - Lab reports, agency records, medical chart abstraction are acceptable
        - Self-report without validation is acceptable
    - HIV viral suppression is a relevant outcome if there is an improvement in viral suppression from pre-to post-intervention
        - Viral suppression levels must be measured using a lab report or medical chart abstraction

No Demonstrated Negative Intervention Effects

- No statistically significant ($p < 0.05$) negative pre-post intervention effect for any relevant outcome
    - A negative intervention effect is defined as a worsening in linkage to, retention in, engagement in, or re-engagement in HIV medical care, ART initiation, or viral suppression post intervention compared to the pre-intervention
- No other statistically significant harmful intervention effect that causes substantial concern

U.S. studies with a comparison arm that did not meet the evidence-based criterion on sample size

- U.S. studies with a comparison arm that did not meet the evidence-based criterion for sample size (i.e., $n \geq 40$ per arm), but have at least 25 participants per study arm will be considered as evidence-informed
- These studies must also demonstrate at least one significant positive intervention effect on a relevant LRC outcome and no significant negative intervention effects

Additional Limitations to Evaluate

- No evidence that additional limitations resulted in considerable bias that reduces the confidence of the findings
- Examples of limitations:
    - Too many post-hoc analyses
    - Inconsistent evidence between effects
    - Inappropriate subset analyses
    - Not accounting for various reasons why participants were not included in the LRC outcome

- For serial cross-sectional studies, there are statistically significant differences in demographic characteristics between “pre” and “post” samples that may introduce bias
- Other notable biases threatening internal or external validity

All criteria must be satisfied for an intervention to be considered an LRC EI.

Structural Interventions (SI) Efficacy Criteria

National HIV prevention goals call for expansion of efforts to prevent HIV infection using a combination of effective, evidence-based approaches. Structural Interventions do not rely on individual behavior change to alter the environment and can be used to enhance the effectiveness of biomedical and behavioral interventions. The SI Best Practices contains two sets of criteria to evaluate interventions: Evidence-based and Evidence-informed, which were developed between 2016 and 2017 by were after numerous consultations with CDC scientists who have expertise in HIV prevention and structural interventions. Criteria were last updated October 26, 2020.

Evidence-Based Interventions	Evidence-Informed Interventions
• Evaluate interventions with a comparison arm • Sample size is ≥ 40 per arm • Demonstrate significant positive effects for improving SI outcomes SI EBIs provide the **strongest** evidence of efficacy.	• Evaluate interventions that have one-group designs and pre-post data • Evaluate interventions with a comparison arm (sample <40 but ≥ 25 per arm) • Demonstrate significant positive effects for improving SI outcomes SI EIs have **some evidence** of working and need further testing with a comparison group or larger samples.

Criteria for SI Evidence-Based Interventions

Intervention Description

- Clear description of key aspects of the intervention

Quality of Study Design*

- Prospective study design
- Appropriate and concurrent comparison arm (provided it is similar to intervention arm with respect to population, setting, and time frame, and identical with respect to follow-up interval, recall period, and outcome measures; or adjusted analysis)
- Random, minimally biased, or moderately biased allocation of participants to study arms, allowing for selection bias unrelated to the intervention or HIV risk. Assignment may be based on pre-established groups or selection into something other than the intervention, provided neither is directly related to HIV risk.
    - For a study that grouped units of assignment (e.g., individual, couple, personal network) into larger groups for delivery of the intervention, analysis should be adjusted for the potential cluster effect or intraclass correlation (ICC) among participants receiving the intervention

together, unless there are only two groups, or studies report that the ICC was small enough (estimated to be <0.10) that adjustment was unnecessary.

Quality of Study Implementation and Data Analysis

- Follow-up assessment ≥ 3-months post completion of intervention for each study arm with recall not referring to pre-intervention period
  Note: This criterion is not applicable for engagement in, linkage to, retention in, and re-engagement in care outcomes, HIV testing, antiretroviral treatment (ART) uptake, Pre-exposure prophylaxis (PrEP)-related outcomes, AIDS mortality
- Comparison between intervention arm and an appropriate comparison arm
- Analysis of participants in study arms as originally allocated regardless of contamination or logistic/implementation issues
  Note: Data from contaminated participants may be excluded if numbers are small, but participants may not be re-assigned for analytic purposes
- Analysis of participants regardless of the level of intervention exposure
  Note: Participants exposed to < 50% of the entire intended intervention may be excluded
- Use of appropriate cluster-level analyses if assigned to study arms by cluster or group
- Analysis must be based on post-intervention levels or on pre-post changes in measures between groups
  Note: If pre-post changes are used in analysis, measures must be identical, including identical recall period
- Analysis is based on an $\alpha = .05$ (or more stringent) and a 2-sided test
- With nonrandomized assignment, either no statistical differences in baseline levels of the outcome exist or baseline differences are statistically controlled for in the analysis
  - If moderately biased assignment was used, differences in baseline demographics must be controlled for in the analysis.
- Analytic sample ≥ 40 participants per study arm
  - Note: Studies that meet all evidence-based criteria with the exception of sample size (i.e., n ≥ 40 per arm), and have at least 25 participants per study arm will be considered as evidence-informed (see Structural Evidence-Informed [EI] criteria).

Strength of Evidence

Demonstrated Significant Positive Intervention Effects

- Positive and statistically significant ($p < .05$) intervention effect for ≥1 relevant outcome measure
- A positive intervention effect is defined as:
  - a greater reduction (or lower increase) in HIV/STD incidence, risk behaviors or HIV-related stigma;
  - a greater increase in HIV protective behaviors (including HIV testing, PrEP-related behaviors);
  - greater improvement in, or higher level of, a medication adherence-related behavioral or biologic outcome (including viral suppression);
  - a greater increase in ART or PrEP prescriptions by providers; or
  - greater improvement in engagement in, linkage to, retention in, engagement or re-engagement in HIV medical care in the intervention arm relative to the comparison arm
- A relevant outcome is defined as:

- Sex risk behaviors (e.g., abstinence, mutual monogamy, number of sex partners, consistent condom use with anal/vaginal sex, condomless anal/vaginal sex, proportion of anal/vaginal sex acts protected, refusal to have unsafe sex) directly impacting HIV risk
- Drug injection behaviors (e.g., frequency of injection drug use, needle sharing)
- PrEP-related:
  - Screening for PrEP eligibility and referring to PrEP services: assessed HIV risk behavior to identify participants as eligible PrEP candidates and referred them to PrEP services (e.g., scheduled the first PrEP service appointment)
  - Linkage to PrEP care: a participant completed a healthcare visit that includes being prescribed PrEP
  - PrEP initiation/uptake: initiation of PrEP among PrEP-naïve participants or those who were not PrEP users as defined by study authors via self-report or medical or pharmacy records (e.g., filled a prescription for PrEP, started PrEP)
  - PrEP use: on PrEP (including lifetime, current use) based on self-report or medical or pharmacy records
  - PrEP medication adherence or persistence: taking PrEP on a regularly agreed to schedule (e.g., daily dose, on demand) measured by electronic data monitoring (e.g., Medication Event Monitoring System [MEMS] caps), pill count, pharmacy refill, self-reported adherence, or medical record
  - PrEP drug levels: based on assays that assess PrEP drug or drug metabolite levels in plasma, urine, hair, or dried blood spots
  - Retention in PrEP care: completed PrEP medical visit(s) over a period of time (e.g., attended one visit every 3 months for at least 6 months) that is self-reported or documented in medical records
  - PrEP at the system or community level (e.g., number of people on PrEP assessed at the healthcare system or community level)
- ART or PrEP prescriptions (as outcomes of provider interventions only; self-reported by provider or documented in medical or pharmacy records)
- HIV-related stigma
- Medical mistrust
- HIV testing (e.g., utilization of HIV C&T services, repeat testing, self-testing)
  - Note: HIV testing is a relevant outcome only if the study reports new HIV infections
- a medication adherence outcome measure that may include electronic data monitoring (e.g., MEMs caps), pill count, pharmacy refill, or self-reported adherence
- a biologic measure indicating HIV or STD (e.g., prevalence or incidence measures of hepatitis, HIV, or other STDs)
  - Note: Biologic measures of STD infections are relevant outcomes only as a proxy for HIV behavior
- HIV morbidity or AIDS mortality (includes biologic measures of HIV viral suppression or CD4 count)
- HIV medical care visit – measures of a completed outpatient primary HIV medical care visit or HIV viral load and/or CD4 count when used as proxies for a HIV medical care visit
  - For *engagement in care*, a relevant outcome is having one completed HIV medical visit
  - For *linkage to care*, a relevant outcome is the completed first HIV medical visit for newly diagnosed HIV-positive persons

        - For *retention in care*, a relevant outcome is having completed multiple HIV medical visits over a period of time
        - For *re-engagement in care*, a relevant outcome is the completed HIV medical visit for persons who were lost to or inconsistent in care
            - Note: Completed HIV medical visits must be documented in medical records, administrative or agency records, or surveillance reports
            - Note: Self-reports of completed medical visits validated by medical records; administrative or agency records are also acceptable
- In summary, the effect must be:
    - reported at the required follow-up
    - based on the quality of the study design
    - based on the study implementation and analysis

No Demonstrated Significant Negative Intervention Effects

- No negative and statistically significant ($p < .05$) intervention effect for any relevant outcome
    - A negative intervention effect is defined as:
        - a greater increase in HIV/STD incidence, risk behaviors, HIV-related stigma or medical mistrust;
        - a greater decrease in HIV protective behaviors (including HIV testing, PrEP-related behaviors);
        - greater reduction in, or lower level of, a medication adherence-related behavioral or biologic outcome;
        - greater decrease in ART or PrEP prescriptions by providers; or
        - lower level of engagement in, linkage to, retention in, or re-engagement in HIV medical care
        - in the intervention arm relative to the comparison arm

Additional Limitations to Evaluate

- No evidence that additional limitations resulted in a fatal flaw:
    - A fatal flaw has occurred when the overall evaluation of limitations indicates they resulted in considerable bias, thus substantially reducing the confidence of the findings.
    - Examples of item limitations to check for possible fatal flaw:
        - Effects only found within potentially biased subset analyses
        - Substantial missing data. Missing data plus loss to attrition exceeds acceptable limits for
        - retention alone (≥ 40%)
            - Note: This criterion is not applicable for engagement in, linkage to, retention in, and reengagement in care outcomes, HIV testing, antiretroviral treatment (ART) uptake, linkage to PrEP care, retention in PrEP care, PrEP prescribing behavior, PrEP utilization, or AIDS mortality
        - Study arm non-equivalence: statistically significant differences between arms in important baseline demographics or risk factors
        - Differential retention: (1) significant difference between study arms in characteristics among retained or attrited participants; OR (2) more than minimal rate of differential retention (>10%)

- Note: This criterion is not applicable for engagement in, linkage to, retention in, and reengagement in care outcomes, HIV testing, ART uptake, linkage to PrEP care, retention in PrEP care, PrEP prescribing behavior, PrEP utilization, or AIDS mortality
- Intervention activities did not match with the intervention concepts or guiding theories intended to produce the desired outcomes
- Report does not clearly describe issues related to generalizability
- Too many post hoc analyses (even with Bonferroni corrections)
- Inconsistent findings between effects

*Additional study designs (e.g., before/after study design) will be evaluated as Structural Evidence-Informed Interventions (EIs).

All criteria must be satisfied for an intervention to be considered a Structural EBI.
Adapted from: Lyles et al., (2006), Lyles et al., (2007), Higa et al., (2016), Sipe et al., (2017).

Criteria for SI Evidence-Informed Interventions

Intervention Description

- Clear description of key aspects of the intervention

Quality of Study Design

For before/after studies

- Evaluates data before and after intervention implementation in studies without a comparison arm

For two-group studies with a comparison arm that did not meet the evidence-based criterion on sample size

- Studies with a comparison arm that met all evidence-based criteria with the exception of sample size (i.e., $n \geq 40$ per arm) and have at least 25 participants per study arm will be considered as evidence-informed

Quality of Study Implementation and Analysis

- Analysis must be based on pre-post changes or post-intervention levels
  - Note: For pre-post changes used in analysis, measures must be identical, including identical recall period
- Analysis based on an $\alpha = .05$ (or more stringent) and a 2-sided test

Strength of Evidence

Demonstrated Significant Positive Intervention Effects

- Statistically significant ($p < .05$) positive pre-post intervention effect for ≥ 1 relevant outcome measure
- A positive intervention effect is defined as:
  - Greater reduction (or lower increase) in HIV/STD incidence, risk behaviors, HIV-related stigma or medical mistrust
  - Greater increase in HIV protective behaviors (including HIV testing, PrEP-related behaviors)

- Greater increase in ART or PrEP prescriptions by providers
- Greater improvement in, or higher level of, a medication adherence-related behavioral or biologic outcome (including viral suppression); or
- Greater improvement in engagement in, linkage to, retention in, or re-engagement in HIV medical care post intervention versus pre intervention

- A relevant outcome is defined as:
  - Sex risk behaviors (e.g., abstinence, mutual monogamy, number of sex partners, consistent condom use with anal/vaginal sex, condomless anal/vaginal sex, proportion of anal/vaginal sex acts protected, refusal to have unsafe sex) directly impacting HIV risk
  - Drug injection behaviors (e.g., frequency of injection drug use, needle sharing)
  - PrEP-related:
    - Screening for PrEP eligibility and referring to PrEP services: assessed HIV risk behavior to identify participants as eligible PrEP candidates and referred them to PrEP services (e.g., scheduled the first PrEP service appointment)
    - Linkage to PrEP care: a participant completed a healthcare visit that includes being prescribed PrEP
    - PrEP initiation/uptake: initiation of PrEP among PrEP-naïve participants or those who were not PrEP users as defined by study authors via self-report or medical or pharmacy records (e.g., filled a prescription for PrEP, started PrEP)
    - PrEP use: on PrEP (including lifetime, current use) based on self-report or medical or pharmacy records
    - PrEP medication adherence or persistence: taking PrEP on a regularly agreed to schedule (e.g., daily dose, on demand) measured by electronic data monitoring (e.g., MEMS caps), pill count, pharmacy refill, self-reported adherence, or medical record
    - PrEP drug levels: based on assays that assess PrEP drug or drug metabolite levels in plasma, urine, hair, or dried blood spots
    - Retention in PrEP care: completed PrEP medical visit(s) over a period of time (e.g., attended one visit every 3 months for at least 6 months) that is self-reported or documented in medical records
    - PrEP at the system or community level (e.g., number of people on PrEP assessed at the healthcare system or community level)
  - ART or PrEP prescriptions (as outcomes of provider interventions only)
  - HIV-related stigma
  - Medical mistrust
  - HIV testing (e.g., utilization of HIV C&T services, repeat testing)
    - Note: HIV testing is a relevant outcome only if the study reports new HIV infections
  - Medication adherence outcome measure that may include electronic data monitoring (e.g., MEMs caps), pill count, pharmacy refill, or self-reported adherence
  - Biologic measure indicating HIV or STD (e.g., prevalence or incidence measures of hepatitis, HIV, or other STDs)
    - Note: Biologic measures of STD infections are relevant outcomes only as a proxy for HIV behavior
  - HIV morbidity or AIDS mortality (includes biologic measures of HIV viral suppression or CD4 count)
  - HIV medical care visit – measures of a completed outpatient primary HIV medical care visit or HIV viral load and/or CD4 count when used as proxies for a HIV medical care visit

        - For engagement in care, a relevant outcome is having one completed HIV medical visit
        - For linkage to care, a relevant outcome is the completed first HIV medical visit for newly diagnosed HIV-positive persons
        - For retention in care, a relevant outcome is having completed multiple HIV medical visits over a period of time
        - For re-engagement in care, a relevant outcome is the completed HIV medical visit for persons who were lost to or inconsistent in care
            - Note: Completed HIV medical visits must be documented in medical records, administrative or agency records, or surveillance reports
            - Note: Self-reports of completed medical visits validated by medical records, administrative or agency records are also acceptable
- In summary, the effect must be:
    - Reported at the required follow-up
    - Based on the quality of the study design
    - Based on the study implementation and analysis

No Demonstrated Significant Negative Intervention Effects

- No negative and statistically significant ($p < .05$) pre-post intervention effect for any relevant outcome
    - A negative intervention effect is defined as:
        - Greater increase in HIV/STD incidence, risk behaviors, HIV-related stigma or medical mistrust; greater decrease in HIV protective behaviors;
        - Greater reduction in, or lower level of, a medication adherence-related behavioral or biologic outcome;
        - Greater decrease in ART or PrEP prescription by providers; or
        - Lower level of engagement in, linkage to, retention in, or re-engagement in HIV medical care in the intervention arm relative to the comparison arm or post intervention versus pre intervention

Additional Limitations to Evaluate

- No evidence that additional limitations resulted in considerable bias that reduces the confidence of the findings
    - Examples of limitations
        - Effects only found within potentially biased subset analyses
        - Too many post-hoc analyses
        - Inconsistent evidence between effects
        - For serial cross-sectional studies, statistically significant differences in demographic
        - characteristics between “pre” and “post” samples that may introduce bias
        - Other notable biases threatening internal or external validity

All criteria must be satisfied for an intervention to be considered a Structural Evidence-Informed intervention (EI).

Structural Intervention Taxonomy
in HIV Prevention

CAPACITY BUILDING
Change that improves ability to provide services or programs

Subcategories:
Provider/Supervisor Training
Technology
Hiring Staff/Funding
Staff Incentives

MASS MEDIA
Widely disseminated interventions via large-scale communication

Subcategories:
Social Marketing
Narrative Interventions

POLICY/ PROCEDURE
Formal guidance, principal, or rule adopted to bring about change

Subcategories:
Institutional Policy/Procedure
Governmental Policy
Legislation

ACCESS
Provision of health products, services or actions to users

Subcategories:
HIV Testing
Condoms
STI Testing
Sterile Injection Equipment
HIV Health Care
Drug Treatment

COMMUNITY MOBILIZATION
A process of change generated and sustained through community interactions

PHYSICAL STRUCTURE
Physical form that affects risk directly or ease in performing healthy behaviors

Subcategories:
Integration of Services
New Physical Structures
Services Provided in Nontraditional Settings

SOCIAL DETERMINANTS OF HEALTH
Addresses basic needs or acceptance and respect

Subcategories:
Survival
Acceptance and Respect

PREVENTION RESEARCH SYNTHESIS

Note. Categories are mutually exclusive with the exception of Access

June 2018

Pre-Exposure Prophylaxis (PrEP) Efficacy Criteria

PrEP taken prophylactically or prior to HIV exposure is proven to prevent HIV acquisition among those exposed through sex or needles. The federal Ending the HIV Epidemic (EHE) initiative highlights PrEP as a key strategy to prevent HIV transmission; therefore, it is important to identify interventions for increasing PrEP use and persistence. These criteria were finalized in March 2020 after consultations with CDC and National Institutes of Health (NIH) subject matter experts. Criteria last updated April 26, 2023.

Evidence-Based Interventions	Evidence-Informed Interventions
• Evaluate interventions with a comparison arm • Sample ≥ 40 per arm • Demonstrate significant positive effects for improving PrEP use and persistence Interventions are rigorously evaluated and provide the **strongest evidence** of efficacy.	• Evaluated with a comparison arm (sample < 40 but ≥ 25 per arm) or with one-group study designs that have pre-post data. • EIs have shown significant positive effects for improving PrEP use and persistence. Interventions have **some evidence** of working and need further testing with a comparison group.

Criteria for PrEP Evidence-Based Interventions

Intervention Description

- Clear description of key aspects of the intervention

Quality of Study Design*

- 2 or more study arms
- Prospective study design
- Appropriate and concurrent comparison arm (provided it is similar to intervention arm with respect to population, setting, and time frame, and identical with respect to follow-up interval, recall period, and outcome measures; or reports adjusted analysis)
- Random allocation or the use of methods that allocate participants to study arms and do not cause substantial concern. These methods allow for selection bias unrelated to the intervention or HIV risk. Assignment may be based on pre-established groups or selection into something other than the intervention, provided neither is directly related to HIV risk:
    - For a study that arranged units of assignment (e.g., individual, couple, personal network) into larger groups for delivery of the intervention, analysis should be adjusted for the potential cluster effect or intraclass correlation (ICC) among participants receiving the intervention

together, unless there are only two larger groups, or studies report that the ICC was small enough (estimated to be <0.10) that adjustment was unnecessary

Quality of Study Implementation and Data Analysis

- Follow-up assessment
  - ≥ 3-months post initiation of intervention for each study arm for patient-level study
  - at least one post intervention follow-up assessment (no specific follow-up or recall period) for healthcare provider-level or system-level study
- At least a 60% retention rate at a single follow-up assessment in each study arm for screening for PrEP eligibility and referring to PrEP services, PrEP initiation/uptake, PrEP use, PrEP medication adherence or persistence, PrEP drug levels, or HIV incidence
- Comparison between an intervention arm(s) and an appropriate comparison arm(s)
- Analysis of participants in study arms as originally allocated (i.e., participants may not be re-assigned for analytic purposes)
- Data from contamination of participants (e.g., control participants receive intervention) may be excluded if these numbers are small
- Analysis of participants regardless of the level of intervention exposure
  Note: Participants exposed to < 50% of the entire intended intervention may be excluded.
- If participants are excluded due to contamination or low exposure to the intervention, retention rate must acknowledge the exclusion of these participants at each assessment
- Use of appropriate cluster-level analyses if assigned to study arms by cluster or group
- Analysis must be based on follow-up levels or on pre-post changes in measures between study arms
  Note: If pre-post changes are used in analysis, measures must be identical, including identical recall period.
- Analysis is based on a p-value of < 0.05 and a 2-sided test
- With nonrandomized assignment, either no statistical differences in baseline levels of the outcome exist or baseline differences are statistically controlled for in the analysis
- Baseline sample ≥ 40 participants per study arm
  Note: Studies that meet all evidence-based criteria with the exception of sample size (i.e., n ≥ 40 per arm), and have at least 25 participants per study arm at baseline will be considered as evidence-informed interventions

Strength of Evidence

Demonstrated Significant Positive Intervention Effects

- Statistically significant ($p < 0.05$) positive intervention effect for ≥ 1 relevant outcome measure in the intervention arm relative to the comparison arm
  - A positive intervention effect is defined as an improvement in relevant PrEP-related behavioral or biologic outcomes in an intervention arm relative to a comparison arm
  - Relevant PrEP-related behavioral or biological outcomes include:

  <u>PrEP Patient-Level</u>
  - Screening for PrEP eligibility and referring to PrEP services: assessed HIV risk behavior to identify a participant as an eligible PrEP candidate and referred them to PrEP services (e.g., scheduled the first PrEP service appointment)

- Linkage to PrEP care: a participant completed healthcare visit that includes being prescribed PrEP
- PrEP initiation/uptake: initiation of PrEP among PrEP-naïve participants or those who were not PrEP users as defined by study authors via self-report or medical or pharmacy records (e.g., filled a prescription for PrEP, started PrEP)
- PrEP use: on PrEP (including lifetime, current use) based on self-report or medical or pharmacy records
- PrEP medication adherence or persistence: taking PrEP on a regularly agreed to schedule (e.g., daily dose, on demand) measured by electronic data monitoring (e.g., Medication Event Monitoring System caps), pill count, pharmacy refill, self-reported adherence, or medical record
- PrEP drug levels: based on assays that assess PrEP drug or drug metabolite levels in plasma, urine, hair, or dried blood spots
- Retention in PrEP care: completed PrEP medical visit(s) over a period of time (e.g., attended one visit every 3 months for at least 6 months) that is self-reported or documented in medical records
- HIV incidence: HIV infections that are self-reported or documented in medical records

PrEP Healthcare Provider- or System-Level

- PrEP prescribing behavior: self-reported by provider or documented in medical or pharmacy records
- PrEP utilization among health care systems and communities: number of people on PrEP assessed at the healthcare system or community level

No Demonstrated Significant Negative Intervention Effects

- No negative and statistically significant ($p < 0.05$) intervention effects for any PrEP-relevant outcome in the intervention arm relative to the comparison arm.
    - A negative intervention effect is defined as the intervention arm showing:
        - Greater reduction in, or lower level of, PrEP initiation/uptake, PrEP use, PrEP medication adherence or persistence or PrEP drug levels
        - Lower level of screening for PrEP and referring to PrEP services, linkage to PrEP care, retention in PrEP care
        - Greater increase in HIV incidence
        - Lower proportion of PrEP prescribing behavior
        - Lower proportion of people on PrEP assessed at the healthcare system or community level

Additional Limitations to Evaluate

- No evidence that additional limitations resulted in considerable bias that reduces the confidence of the findings
    - Examples of limitations:
        - Too many post-hoc analyses
        - Inconsistent evidence between effects
        - Inappropriate subset analyses

- Not accounting for various reasons why participants were not included in the PrEP outcome
- Not adjusting for cluster effects for studies that allocated individuals to a group-level intervention
- Not accounting for factors that may influence findings (e.g., historical events)
- Other notable biases threatening internal or external validity

*Additional study designs (e.g., before/after study design) will be evaluated with evidence-informed criteria for PrEP.

All criteria must be satisfied for an intervention to be considered a PrEP Evidence-Based Intervention (EBI).

Criteria for PrEP Evidence-Informed (EI) Interventions

Intervention Description

- Clear description of key aspects of the intervention

Quality of Study Design

For before/after studies

- Evaluates data before and after intervention implementation in studies without a comparison arm (e.g., pre/post, historical comparison)

For two-group studies with a comparison arm

- Studies with a comparison arm that met all evidence-based criteria with the exception of sample size (i.e., n ≥ 40 per arm), and have at least 25 participants per study arm at baseline will be considered as evidence-informed interventions

Quality of Study Implementation and Analysis

- Analysis must be based on pre-post changes
  Note: Measures must be identical, including identical recall period
- Analysis based on a p value of < 0.05 and a 2-sided test

Strength of Evidence

Demonstrated Significant Positive Intervention Effects

- Statistically significant ($p < 0.05$) positive intervention effect for ≥ 1 relevant outcome measure
  - A positive intervention effect is defined as an improvement in PrEP-related behavioral or biologic outcomes from pre- to post-intervention
  - Relevant PrEP-related behavioral or biological outcomes are defined as and include:

  PrEP Patient-Level
  - Screening for PrEP eligibility and referring to PrEP services: assessed HIV risk behavior to identify a participant as an eligible PrEP candidate and referred those who were eligible to PrEP services (e.g., scheduled the first PrEP services appointment)
  - Linkage to PrEP care: a participant completed healthcare visit including being prescribed PrEP

- PrEP initiation/uptake: initiation of PrEP among PrEP-naïve participants or those who were not PrEP users as defined by study authors via self-report or medical or pharmacy records (e.g., filled a prescription for PrEP, started taking PrEP)
- PrEP use: on PrEP (including lifetime, current use) based on self-report or medical or pharmacy records
- PrEP medication adherence or persistence: taking PrEP on a regularly agreed to schedule (e.g., daily dose, on demand) measured by electronic data monitoring (e.g., MEMS caps), pill count, pharmacy refill, self-reported adherence, or medical record
- PrEP drug levels: based on assays that assess PrEP drug or drug metabolite levels in plasma, urine, hair, or dried blood spots
- Retention in PrEP care: completed PrEP medical visit(s) over a period of time (e.g., one visit every 3 months for at least 6 months) that is self-reported or documented in medical records
- HIV incidence: HIV infections that are self-reported or documented in medical records

PrEP Healthcare Provider- or System-Level

- PrEP prescribing behavior: self-reported by provider or documented in medical or pharmacy records
- PrEP utilization among health care systems and communities: number of people on PrEP assessed at the healthcare system or community level

No Demonstrated Significant Negative Intervention Effects

- No negative and statistically significant ($p < 0.05$) pre- to post- intervention effects for any PrEP-relevant outcome
  - A negative intervention effect is defined as the post-intervention effect showing:
    - Greater reduction in, or lower level of, PrEP initiation/uptake, PrEP use, PrEP medication adherence or persistence or PrEP drug levels
    - Lower level of screening for PrEP and referring to PrEP services, linkage to PrEP care, retention in PrEP care
    - Greater increase in HIV incidence
    - Lower proportion of PrEP prescribing behavior
    - Lower proportion of people on PrEP assessed at healthcare system or community level

Additional Limitations to Evaluate

- No evidence that additional limitations resulted in considerable bias that reduces the confidence of the findings
  - Examples of limitations
    - Effects only found within potentially biased subset analyses
    - Too many post-hoc analyses
    - Inconsistent evidence between effects
    - For serial cross-sectional studies, statistically significant differences in demographic characteristics between “pre” and “post” samples that may introduce bias
    - Other notable biases threatening internal or external validity

All criteria must be satisfied for an intervention to be considered an effective PrEP Evidence-Informed Intervention (EI).

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