Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations

Web Annex C. Systematic review findings and GRADE tables
Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations

Web Annex C. Systematic review findings and GRADE tables
Contents

Web Annex C. Systematic review findings and GRADE tables 1

Counselling behavioural interventions .............................................................. 1
Chemsex ........................................................................................................... 6
Online service delivery .................................................................................... 16
Peer navigation ............................................................................................... 27
Hepatitis C testing interval and reinfection incidence .................................. 36
Immediate treatment for recent hepatitis C infection .................................... 41
Pooled screening of Chlamydia trachomatis and Neisseria gonorrhoeae ........ 46
Web Annex C. Systematic review findings and GRADE tables

Counselling behavioural interventions

Are counselling interventions to change key populations’ risk behaviour for HIV, STIs and viral hepatitis effective? a systematic review of effectiveness, values and preferences, and cost studies

Systematic review team: Caitlin Kennedy and Teresa Yeh, Johns Hopkins University

Abstract

Background: Key populations – sex workers, men who have sex with men, people who inject drugs, prisoners, and trans and gender diverse individuals – are disproportionately affected by HIV, sexually transmitted infections (STIs), and viral hepatitis (VH). Counselling behavioural interventions are widely used, but their impact on HIV/VH/STI acquisition is unclear.

Methods: To inform World Health Organization guidelines, we conducted a systematic review and meta-analysis of effectiveness, values and preferences, and cost studies published between 1/2010-3/2021. We searched CINAHL, PsycINFO, PubMed, and EMBASE; screened abstracts; and extracted data in duplicate. The effectiveness review included randomized controlled trials (RCTs) with HIV/VH/STI incidence outcomes. We assessed risk of bias using the Cochrane Collaboration tool, generated pooled risk ratios through random effects meta-analysis, and summarized findings in GRADE evidence profiles. Values and preferences and cost data were summarized descriptively.

Findings: We identified 9 effectiveness, 2 values and preferences, and 2 cost articles. Meta-analysis of 6 RCTs showed no statistically significant effect of counselling behavioural interventions on HIV incidence (1,280 participants; combined risk ratio (RR):0.70, 95% confidence interval (CI):0.41 to 1.20) or STI incidence (3,783 participants; RR:0.99; 95% CI:0.74 to 1.31). One RCT with 139 participants showed possible effects on HCV incidence. There was also no effect on secondary outcomes of unsafe (condomless) sex (7 RCTs; 1,811 participants; RR:0.82, 95% CI:0.66 to 1.02) and needle/syringe sharing (2 RCTs; 564 participants; RR 0.72; 95% CI:0.32 to 1.63). There was moderate certainty in the lack of effect across outcomes. Two values and preferences studies found participants liked specific counselling behavioural interventions. Two cost studies found reasonable intervention costs.

Interpretation: While there may be other benefits, the choice to provide counselling behavioural interventions for key populations should be made with an understanding of the potential limitations on incidence outcomes.

Funding: Bill and Melinda Gates Foundation, USAID, PEPFAR

Research in context

Evidence before this study

Previous systematic reviews have suggested that counselling behavioural interventions may reduce HIV/VH/STI risk behaviours among PWID, but no previous systematic reviews have examined their impact across key populations and on HIV/VH/STI acquisition.
**Added value of this study**

This study provides the first synthesis of evidence from rigorous randomized trials on the effect of counselling behavioural interventions for key populations on incidence of HIV, VH, and STIs. Overall, we found no effect of such interventions on HIV/VH/STI incidence. We also evaluated values and preferences and cost data and found it generally favourable.

**Implications of all the available evidence**

While there may be other benefits to such interventions, the choice to include counselling behavioural interventions in standard and minimum packages of interventions for key populations should be made with an understanding of the potential limitations on incidence of these infections.
GRADE evidence profile

GRADE evidence profile for effectiveness review studies - Counselling behavioural interventions

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Nº of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV incidence (follow up: range 3 months to 12 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6,1,2,3,4,5,6,a</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>none</td>
<td>9/790 (1.1%)</td>
<td>10/490 (2.0%)</td>
<td>RR 0.700 (0.409 to 1.197)</td>
<td>6 fewer per 1,000 (from 12 fewer to 4 more)</td>
</tr>
<tr>
<td>HIV/STI incidence (follow up: mean 12 months; assessed with: combined incidence of HIV and four STIs (syphilis, gonorrhoeae, chlamydia, and trichomonas))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,7,f</td>
<td>randomised trials</td>
<td>not serious</td>
<td>serious</td>
<td>not serious</td>
<td>serious</td>
<td>none</td>
<td>26/48.11 (54.0%)</td>
<td>31/47.68 (65.0%)</td>
<td>RR 0.663 (0.224 to 1.960)</td>
<td>219 fewer per 1,000 (from 505 fewer to 624 more)</td>
</tr>
<tr>
<td>STI incidence (follow up: range 6 months to 12 months; assessed with: Combined chlamydia and gonorrhea; sometimes also including trichomoniasis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6,2,3,4,5,8,9,j</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>none</td>
<td>116/1985 (5.8%)</td>
<td>113/1798 (6.3%)</td>
<td>RR 0.965 (0.741 to 1.308)</td>
<td>2 fewer per 1,000 (from 16 fewer to 19 more)</td>
</tr>
<tr>
<td>HCV incidence (follow up: mean 12 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,5,m</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>none</td>
<td>5/77 (6.5%)</td>
<td>9/62 (14.5%)</td>
<td>RR 0.447 (0.158 to 1.267)</td>
<td>80 fewer per 1,000 (from 122 fewer to 39 more)</td>
</tr>
<tr>
<td>HCV incidence (follow up: mean 12 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,5,m</td>
<td>randomised trials</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>none</td>
<td>5/67.24</td>
<td>9/45.25</td>
<td>Rate ratio 0.31 (0.10 to 0.90)</td>
<td>-- per 1000 patient(s) per years (from -- to --)</td>
</tr>
</tbody>
</table>
### Certification assessment

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Other considerations</th>
<th>Counselling behavioural interventions</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>no intervention or a different intervention</td>
<td>(95% CI)</td>
<td>Absolute (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Relative (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Imprecision</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inconsistency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Indirectness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bias</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>none</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Unsafe sex (follow up: range 3 months to 12 months; assessed with: Condomless sex (various measures))

<table>
<thead>
<tr>
<th>№ of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>447/855 (52.3%)</td>
<td>RR 0.821 (0.663 to 1.018)</td>
<td>100 fewer per 1,000 (from 188 fewer to 10 more)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>533/956 (55.8%)</td>
<td>RR 0.719 (0.317 to 1.628)</td>
<td>7 fewer per 1,000 (from 18 fewer to 17 more)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

#### Needle/syringe sharing (follow up: mean 12 months)

<table>
<thead>
<tr>
<th>№ of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>4/374 (1.1%)</td>
<td>RR 0.719 (0.317 to 1.628)</td>
<td>7 fewer per 1,000 (from 18 fewer to 17 more)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

---

**Explanations**

a. Study descriptions: RCTs among MSM/TG, PWID, and SW in China, Kazakhstan, Kenya, and the USA.

b. Risk of bias: Overall Cochrane risk of bias assessment across studies was “some concerns” due to risk of bias in effect of assignment to the intervention (which may lead to deviations from the intended intervention), randomization process, and missing outcome data. However, the biomedical outcome was unlikely to be influenced by knowledge of assignment to the intervention, adherence to the intervention was judged not relevant as the interventions included in this topic already range widely, and retention rates were generally around 90%. Therefore, we did not downgrade for risk of bias.

c. Inconsistency: No statistically significant heterogeneity (Q=1.916, p=0.861, I²=squared = 0.000)

d. Imprecision: Downgraded because (1) 95% CI for RR includes both 1 (no effect) AND either appreciable harm (0.75) or appreciable benefit (1.25), and (2) small number of events with a wide confidence interval.

e. Number of patients: Only includes data for studies that reported this information for this outcome. Two studies that only reported effect sizes but not number of participants with the outcome were included in the meta-analysis but are not included here for the total number of patients. These were Hao et al. 2018 (n=295) and L’Engle et al. 2014 (n=818).

f. Study description: Four arm randomized trial among 584 sex workers who inject drugs in Mexico. Numbers presented here reflect the highest level counseling intervention (interactive injection and sexual risk reduction intervention including video, motivational interviewing, role play) versus the control group.

g. Risk of bias: Cochrane risk of bias assessment was judged as “some concerns” due to assignment to the intervention (which may lead to deviations from the intended intervention) and missing outcome data. However, the biomedical outcome was unlikely to be influenced by knowledge of assignment to the intervention, adherence to the intervention was judged not relevant as the interventions included in this topic already range widely, and retention rates were generally around 88-89% per session. Therefore, we did not downgrade for risk of bias.

h. Inconsistency: Statistically significant heterogeneity (Q=3.863, p=0.049, I²=squared = 74.116) not clearly explainable by subgroup analyses or other reasons.

i. Number of patients: Denominators are person-years, not individual participants.

j. Study descriptions: RCTs among PRIS, MSM/TG, MSM, PWID, and SW in the USA, China, Kazakhstan, and Kenya.

k. Inconsistency: No statistically significant heterogeneity (Q=2.120, p=0.832, I²=squared=0.000)

l. Imprecision: Downgraded once because 95% CI for RR includes both 1 (no effect) AND either appreciable harm (0.75) or appreciable benefit (1.25).
m. Study description: RCT among 300 couples (600 individuals) PWID in Kazakhstan. Couples-based counseling intervention compared to attention-control group on diet and physical activity.

n. Risk of bias: Overall Cochrane assessment for risk of bias was low for this study.

o. Inconsistency: This could not be evaluated, as there is only a single study.

p. Calculated crude RR based on number of events and sample size at baseline.

q. Risk of bias: Overall Cochrane assessment for this study was low risk of bias. However, for this adjusted analysis, it was unclear whether the adjustment was part of the original protocol; it may have been a post-hoc adjustment.

r. Risk ratio: Incidence rate ratio calculated using a covariance adjustment using a baseline measure of unsafe injection in the past 90 days. The study has no published protocol, so it is unclear if this adjustment was part of the original analysis plan or was a post-hoc analysis.

s. Study descriptions: RCTs among PRIS, MSM, PWID, and SW in the USA, China, Kazakhstan, and Kenya.

t. Risk of bias: Overall Cochrane risk of bias assessment across studies was “some concerns” due to risk of bias in effect of assignment to the intervention (which may lead to deviations from the intended intervention), randomization process, and missing outcome data. While adherence to the intervention was judged not relevant as the interventions included in this topic already range widely, retention rates were generally around 90%, the outcome was self-reported and potentially influenced by knowledge of the assignment. Therefore, we downgraded once for risk of bias.

u. Inconsistency: Statistically significant heterogeneity (Q=22.015, p=0.001, I-squared=72.746) not clearly explainable by subgroup analyses. However, for this adjusted analysis, we were unclear whether the adjustment was part of the original protocol or was a post-hoc analysis.

v. Number of patients: Only includes data for studies that reported this information for this outcome. Four studies that only reported effect sizes but not number of participants with the outcome were included in the meta-analysis but are not included here for the total number of participants. These were Eaton et al. 2018 (n=600), El Bassel et al. 2011 (n=282), El Bassel et al. 2014a (n=306), and El Bassel et al. 2014b (n=600 couples).

x. Inconsistency: No statistically significant heterogeneity (Q=1.135, p=0.287, I-squared=11.909) but are not included here for the total number of participants. This was El Bassel et al., 2014b (n=300 couples).

References


Chemsex

Do behavioural interventions increase uptake of services and reduce harms associated with chemsex?

Systematic review team: Caitlin Kennedy and Teresa Yeh, Johns Hopkins University

Background

In 2020, 65% of the 1.5 million new HIV infections globally were predominantly among key populations and their sexual partners – and key populations accounted for 93% of new HIV infections outside of sub-Saharan Africa, and 35% within sub-Saharan Africa (UNAIDS, 2021). In high-income settings, people who inject drugs (PWID) are thought to be responsible for over 80% of ongoing hepatitis C virus (HCV) transmission (De Angelis et al., 2009; Grebely et al., 2014; Williams et al., 2011), including in prisons (Wirtz et al., 2018), and in low- and middle-income countries, transmission among PWID, sex workers (SW) and men who have sex with men (MSM) contributes to hepatitis B virus (HBV) and HCV epidemics as well (Nelson et al., 2011; Scheibe et al., 2020). WHO advocates for sexually transmitted infection (STI) interventions, including strengthening surveillance and screening to be targeted to groups at higher risk (UNAIDS and WHO, 2012; WHO, 2021).

“Chemsex” is a growing phenomenon where individuals engage in sexual activity while taking stimulant drugs such as methamphetamine or mephedrone, typically involving multiple participants, the use of multiple drugs together (including injecting drug use), and over a prolonged time e.g. group sex or orgy parties (Harm Reduction International, 2021; McCall et al., 2015; Schreck et al., 2021). Chemsex is also known by other names, such as slam sex, party and play, and sexualised drug use. It is increasingly reported in some MSM communities (McCall et al. 2015), most often in high income settings in Europe and North America, though a recent qualitative scoping review of sexualized drug use and chemsex among MSM and transgender women found it to be increasingly common in Asia (Maxwell et al., 2019; Newland and Kelly-Hanku, 2021). The associate editor of NEJM Journal Watch Infectious Diseases commented in 2018 that the “markedly high rate” of infections among MSM participating in chemsex in a London study (Pakianathan et al., 2018) “identifies a high-priority (but often challenging) population for prevention efforts (including pre- and postexposure prophylaxis, mental health, chemical health, health promotion, and harm minimalization interventions)” (Henry, 2018).

Chemsex may be associated with unsafe (condomless) sex, which may increase the risk of HIV, HCV and STIs, as well as drug dependence and adverse mental health outcomes (Tomkins et al., 2019). One recent systematic review found that prevalence of HIV-positive MSM engaging in “slam sex” ranged widely between studies, between 0.6 to 100%; HCV prevalence among “slam sex” participants ranged from 3 to 100% (Schreck et al., 2021). Behavioural interventions, such as targeted messages through social media channels, may reduce this risk.

While the 2014/2016 WHO Consolidated Key Populations Guidelines include valid recommendations for both condoms and lubricant for the prevention of sexual transmission of HIV and STIs and provision of sterile needle/syringes for prevention of HIV and viral hepatitis (VH), there is no current recommendation for behavioural interventions which aim to reduce risk behaviours associated with chemsex or to increase use of HIV, VH and STI services among people engaged in chemsex.

Methods

For the purposes of this review, we define chemsex as sexual activity after taking cathinones, methamphetamines, mephedrone, gamma-butyrolactone/gamma-hydroxybutyrate (GBL/GHB), ketamine, or cocaine.
We conducted a systematic review of the evidence in three related areas: effectiveness of the intervention, values and preferences of clients and health workers related to the intervention, and costs or cost-effectiveness of the intervention.

**Effectiveness review**

The effectiveness review was designed according to the PICO form as follows: Do behavioural interventions increase uptake of services and reduce harms associated with chemsex?

- **Populations:** Any populations who engage in chemsex
- **Interventions:** Behavioural interventions
  
  *We define behavioural interventions as any intervention that is attempting to change behaviours to reduce risk of HIV/VH/STI acquisition or transmission. This includes pre-exposure prophylaxis (PrEP) as an intervention, as well as interventions to increase PrEP uptake or willingness to use PrEP.*
- **Comparator:** No behavioural intervention
- **Outcomes:**
  
  **Primary outcomes:**
  1. Use of prevention services (e.g. PrEP uptake, PrEP adherence, PEP uptake, post-exposure prophylaxis (PEP) adherence, counselling, condoms)
  2. Uptake of testing services for HIV/VH/STIs
  3. HBV incidence
  4. HCV incidence
  5. HIV incidence
  6. STI incidence (e.g. syphilis, gonorrhoea)

  **Secondary outcomes:**
  7. Unsafe sex (e.g. condomless sex, sex without lubricant, sex without PrEP)
  8. Needle/syringe sharing
  9. Mental health issues (e.g. suicide, depression)
  10. Non consensual sex and other sexual violence
  11. Mortality

**Inclusion criteria for this review were as follows:**

1. **Study design:** Randomized controlled trials (RCTs) or observational studies that compared the intervention vs. the comparison
2. **Measured one or more of the outcomes of interest**
3. **Published in a peer-reviewed journal from January 1, 2010 through the search date of May 27, 2021**

No restrictions were placed based on location of the intervention or language of the publication.

We searched four databases (CINAHL, PsycINFO, PubMed, and EMBASE) for relevant peer-reviewed publications. Search terms covered terms for key populations, infections (HIV, VH, STIs), and peer navigator interventions. The full search strategy for PubMed is available in the Appendix; this was adapted to other databases. This search was complemented by several other ways of identifying articles. First, we ran two earlier searches for behavioural interventions for key populations more broadly – one in 2019 as part of an original scoping review (although this did not include specific search terms for chemsex), and one in March 2020 as part of a search just for RCTs. Articles identified through these prior searches were included in the review. Second, we hand-searched the references of articles identified for inclusion in the review. Third, we contacted experts in the field (including guideline development group members) to identify any additional articles we may have missed. Finally, we conducted an additional search just on PubMed using the search term
“chemsex” without any additional terms on June 26, 2021, and screened all articles identified in
that search.
Titles, abstracts, citation information, and descriptor terms of citations identified through the
search strategy were screened for initial inclusion. Full text articles were obtained of all selected
abstracts and two independent reviewers assessed all full-text articles for eligibility to determine
final study selection. Differences were resolved through consensus. Data were extracted
independently by two reviewers using standardized data extraction forms in Excel. Differences
in data extraction were resolved through consensus and referral to a senior study team member
when necessary.

The following information was gathered from each included study in the effectiveness review:

- citation information (author, year, title, journal, language of article)
- location (country, urban/rural, World Bank income classification, WHO region)
- key population (MSM, PWID, SW, trans and gender diverse people (TGD), prisoners (PRIS))
  and description (gender, age, chemsex activity)
- sample size (n)
- study design (specific study design; RCT vs observational; follow-up periods and loss to
  follow-up)
- intervention summary and longer description (including who delivered intervention, where
  intervention was provided, how long/frequent intervention was)
- comparator description
- study outcomes (check box based on PICOs above)
- study outcomes (analytic approach, outcome measures/definitions, intervention vs
  comparison group, n/% or effect sizes with confidence intervals or significance levels,
  conclusions, limitations)

For randomized trials, risk of bias would have been assessed using the Cochrane Collaboration’s
tool for assessing risk of bias (Sterne et al., 2019). Methodological components of the studies would
have been assessed and classified as high or low risk of bias. For studies that were not randomized
trials but were comparative, study rigor would have been assessed using the Evidence Project
8-item checklist for intervention evaluations (Kennedy et al., 2019) and ROBINS-I (Sterne et al.,
2016).

We planned to analyse data according to coding categories and outcomes. Where there were
multiple studies reporting the same outcome for the same intervention-comparator comparison
for the same population, we planned to conduct meta-analysis using random effects models,
stratified by key population.

Values and preferences review
The same search terms were used to search and screen for studies to be included in the values and
preferences review. Studies were included in this review if they presented primary data examining
the values and preferences of potential beneficiaries, communities, providers, and stakeholders
for behavioural interventions for chemsex. These studies could be qualitative or quantitative in
nature, but had to present primary data collection – think pieces and review articles were not
included. Values and preferences literature was summarized qualitatively and was organized by
study design and methodology, location, and population.

Cost and resource needs
The same search terms were used to search and screen for studies to be included in the cost
review. Studies were included in this review if they presented primary data comparing costing,
cost-effectiveness, cost-utility, or cost-benefit of the intervention and comparison listed in the
PICO question above, or if they presented cost-effectiveness of the intervention as it relates to the
PICO outcomes listed above. We planned to summarize cost literature summarized qualitatively. We planned to organize cost literature into four categories (health sector costs, other sector costs, patient/family costs, and productivity impacts) and within each category present it by study design/methodology, location, and population.

Findings are presented separated by effectiveness, values and preferences, and cost reviews.

Results

Figure 1 presents the flow chart showing inclusion of articles in the systematic review. We identified 0 articles meeting the inclusion criteria for the effectiveness review, 5 for values and preferences, and 0 for costs.

Though extant literature on chemsex has grown in the last several years, most articles focus on describing characteristics of people who partake in chemsex, making associations between chemsex and other sociodemographic factors or risk behaviours (e.g. condomless anal sex, injection drug use) or clinical outcomes. Though some who work in this field distinguish chemsex from sexualized drug use (Harm Reduction International, 2021), we were open to including any article that feasibly assessed the effectiveness of, values and preferences related to, costs of interventions designed to mitigate harms associated with chemsex. However, none of the identified articles described interventions designed to reduce risks associated with chemsex. As noted in an informal email communication with expert Dr. Anders Boyd, “most of the interventions to date do not actually focus on only chemsex, but rather chemsex as one of many behaviours that could be targeted” (referring to his own work with Dr. Karine Lacombe in Amsterdam, the Swiss HCVree program, and the ICECREAM study).

Figure 1. Flow chart showing inclusion of articles across the stages of the systematic review

- **Identification**
  - # of records identified through database searching (N=290)
  - # of records after duplicates removed (N=247)

- **Screening**
  - # of records screened at first level (one person) (N=247)
  - # of abstracts screened at second level (two people) (N=53)

- **Eligibility**
  - # of full-text articles retrieved to determine eligibility (N=7)
  - Articles excluded after full-text review (N=2) because:
    - No key populations (N=1)
    - No behavioral intervention targeting chemsex (N=1)

- **Included**
  - Studies included in the systematic review (N=5)
    - PICO: 0
    - VP: 5
    - Cost: 0
  - # of additional records identified through other sources (N=4)
  - # of records after duplicates removed (N=247)
  - # of abstracts screened at second level (two people) (N=53)
  - # of records excluded (N=194)
  - # of records excluded (N=46)
Values and preferences review

Overall, 5 studies were included in the values and preferences review. Table 1 provides descriptive data for these studies as well as key finding. All were conducted among MSM in high-income countries: two in the UK, one in Belgium, one in Australia, and one in Singapore.

<table>
<thead>
<tr>
<th>Study</th>
<th>Location Population Study Design Methods Sample size (n)</th>
<th>Key values and preferences findings</th>
</tr>
</thead>
</table>
| Tomkins et al., 2018 | UK: Greater Manchester MSM Quantitative Online survey with open-ended responses N=52 | • Preferred location to access services (“advice or support about your drug use”)  
  • 41/52 (79%): specialist chemsex service within a sexual health clinic  
  • 10/52 (19%): voluntary sector  
  • 1/52 (2%): standard drug service  
  • 0/52 (0%): outreach clinic in a bar/club/sauna  
  • Experiences with existing services:  
    • 4/52 (8%) had already accessed support for their chemsex use  
    • Good things about these services: ‘non-judgmental attitude’, ‘gained advice about the chems addiction, affects what meds I’m on etc.’  
    • What could be improved about these services: ‘availability and publicity directed at the correct demographic’  
  • Barriers to accessing support  
  • Drug use ‘being known’; feeling of being in control of drug use |
| Bedi et al., 2020 | Australia: North Sydney MSM Quantitative Online survey N=30 | Responses about a patient information leaflet designed to provide basic information on the effects of chemsex drugs, safety tips and resources for additional support services  
  • 19/27 (70%) said that they would use the information in the chemsex patient information leaflet to support their own harm reduction  
  • 17/27 (63%) said that they would use the information to help or inform a sexual partner or friend  
  • 18/27 (67%) stated that they had learned something new  
  • 3/27 (11%) said that they would use the information to change their current drug use behaviour |
| Herrijgers et al., 2020 | Belgium MSM Qualitative In-depth interviews N=20 | Respondents highlighted needs including:  
  • Reliable and easily-accessible information (to avoid conflicting/unreliable information on the internet), particularly information about emergency help in case of an overdose or harmful drug interactions. Other useful information respondents mentioned concerned: drug effects, correct dosage of drugs, information specific to injection of drugs, chemsex related risks, safer sex guidelines, and symptoms of STIs.  
  • Anonymous medical and psychological healthcare support  
  • Chemsex-specific care  
  • A value-neutral safe space to talk about chemsex experiences |
<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Population</th>
<th>Study design</th>
<th>Methods</th>
<th>Sample size (n)</th>
<th>Key values and preferences findings</th>
</tr>
</thead>
</table>
| Bourne et al., 2015        | UK: South London  | MSM        | Qualitative        | In-depth interviews           | N=30           | • Half had never accessed any professional support and those who had usually only accessed drugs information websites. A small number had accessed psychotherapeutic services, usually in community-based settings, and they valued the opportunity to talk through options to better manage their engagement in chemsex, rather than being told they had to abstain.  
• Regardless of modality, MSM valued clear, honest and nonjudgmental advice about engaging in chemsex and how to manage potential harms.  
• Most participants had not sought out specialist drug services because they were concerned that they might be ill-equipped to discuss chemsex among gay men, and its associated context and costs and benefits. Some had concerns about disclosing their sexuality or, more commonly their sexual activity under the influence of drugs to others who may have limited cultural understanding.  
• When asked to consider where they would feel most comfortable accessing drug information or harm reduction services relating to chemsex, the vast majority said they would prefer to visit a sexual health service. They had come to know and trust these organisations as gay friendly and staffed by individuals aware of the social and cultural context of gay sex.  
• Finally, more than a quarter of participants expressed a desire to see more combined drug harm reduction and sexual health services, where specialist skills could address the holistic health needs of gay men. |
| Tan et al., 2018           | Singapore         | MSM        | Qualitative        | In-depth interviews           | N=30           | • MSM suggested using gay-specific commercial venues as avenues for awareness and educational campaigns (entities like gay bars and sex-on-premises venues (e.g. saunas))  
• Participants felt more could be done to reach young gay and bisexual men in Singapore through social media, which could potentially increase the reach of awareness campaigns focusing on HIV prevention and drug use.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

Several studies assessed experiences with existing services or preferences about receiving services about chemsex.  

In the UK, Tomkins et al. (2018) found that the most preferred location to access “advice or support about your drug use” was specialist chemsex services within a sexual health clinic (41/52: 79%). A smaller number selected voluntary sector (10/52: 19%), while standard drug service and outreach clinic in a bar/club/sauna were not preferred. In terms of experiences with existing services, 4/52 (8%) had already accessed support for their chemsex use. In open-ended responses, good things about these services included: ‘non-judgmental attitude’, ‘gained advice about the chems addiction’. Things that could be improved about these services were: ‘availability and publicity directed at the correct demographic’. Barriers to accessing support included drug use ‘being known’, and feeling in control of drug use.  

A second, qualitative study in the UK (Bourne et al., 2015) similarly found that MSM valued clear, honest and nonjudgmental advice about engaging in chemsex and how to manage potential harms. Most participants had not sought out specialist drug services because of the perceived limited cultural understanding or participants’ reluctance to disclose sexuality or, more commonly,
drug use. The majority preferred sexual health service for chemsex-related information and services as they were trusted as being gay-friendly. A quarter expressed a desire for combined drug harm reduction and sexual health services.

Another qualitative study in Belgium (Herrijgers et al., 2020) also found MSM wanted reliable and easily-accessible information, anonymous medical and psychological healthcare support, chemsex-specific care (e.g. specialized counseling with a single professional about both drug and sex related questions), and a value-neutral safe space to talk about chemsex experiences.

One study from Singapore explored more broadly services for chemsex. MSM suggested using gay-specific commercial venues as avenues for awareness and educational campaigns, and social media to reach out to younger gay and bisexual MSM.

Finally, one study from Australia (Bedi et al., 2020) created a patient information leaflet designed to provide basic information on the effects of chemsex drugs, safety tips and resources for additional support services. They conducted a brief online survey to evaluate the leaflet. Of 27 MSM participants, 14 (52%) reported using a recreational drug during sex in the previous six months. 19/27 (70%) said they would use the information in the chemsex patient information leaflet to support their own harm reduction, while 17/27 (63%) said they would use the information to help or inform a sexual partner or friend. 18/27 (67%) had learned something new, and 3/27(11%) would use the information to change their current drug use behaviour.

Cost review

No studies presented primary data examining cost-effectiveness, cost-utility, or cost-benefit for behavioural interventions for chemsex.

References


Appendix: Search Strategy

Concept 1: Key populations

Concept 1a: SW

OR

Concept 1b: MSM

OR

Concept 1c: PWID

OR

Concept 1d: TGD

OR

Concept 1e: PRIS

OR

Concept 1f: general key pops terms
(key population [tw] OR most at risk population [tw] OR MARPS [tw] OR vulnerable population [tw])

AND

Concept 2: HIV, Viral Hepatitis, STIs

AND

Concept 3: Chemsex
Online service delivery

Question: Does providing services online improve uptake of HIV/VH/STI prevention, testing, linkage to treatment and treatment retention for key populations?

Systematic review team: Teresa Yeh and Caitlin Kennedy, Johns Hopkins University

Abstract

Background: Despite the growth of online interventions for HIV, viral hepatitis (VH), and sexually transmitted infections (STIs) for key populations, the evidence for the effectiveness of these interventions has not been synthesized.

Objectives: To inform World Health Organization (WHO) guidelines for HIV/VH/STI service delivery for key populations, we systematically reviewed the effectiveness, values and preferences, and costs of online outreach, online case management, and targeted online health information for key populations (men who have sex with men, sex workers, people who inject drugs, trans and gender diverse people and people living in prisons).

Methods: We searched CINAHL, PsycINFO, PubMed, and EMBASE for peer-reviewed studies; screened abstracts; and extracted data in duplicate. The effectiveness review included randomized controlled trials (RCTs) and observational studies. We assessed risk of bias using the Cochrane Collaboration tool for RCTs and the Evidence Project and ROBINS-I tools for non-RCTs. Values and preferences and cost data were summarized descriptively.

Results: Of 2,711 records identified, we included 13 articles in the effectiveness review (3 for online outreach, 7 for online case management, and 3 for targeted online health information), 15 articles in the values and preferences review, and one article in the costs review. Nearly all were conducted among men who have sex with men in the United States. These articles provided evidence that online approaches are as effective as face-to-face services in terms of reaching new people, use of HIV/VH/STI prevention services, linkage to and retention in HIV care. Among men who have sex with men in the United States, such interventions were considered feasible and acceptable. One cost study among Canadian men who have sex with men found that syphilis testing campaign advertisements had the lowest cost-per-click ratio on “hook-up” platforms compared to more traditional social media platforms.

Conclusions: Online services for HIV/VH/STIs may be a feasible and acceptable approach to expanding services to key populations with similar outcomes as standard of care, but more research is needed in low-resource settings, among key populations other than men who have sex with men, and with infection focuses other than HIV.
## GRADE evidence profile

**GRADE evidence profile for effectiveness review studies - Outreach through online platforms**

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>Nº of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nº of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Previously unreached people getting reached (follow up: 6 months; assessed with: Number of contacts with MSM by public health dept)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>observational studies</td>
<td>serious&lt;sup&gt;b&lt;/sup&gt;</td>
<td>not serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>not serious</td>
</tr>
<tr>
<td><strong>Use of prevention services (follow up: range 3 months to 12 months; assessed with: condom use, self-reported)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>not serious</td>
</tr>
<tr>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>not serious</td>
</tr>
<tr>
<td><strong>Use of prevention services (follow up: mean 6 months; assessed with: consistent condom use, self-reported, with main male sex partner)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;g&lt;/sup&gt;</td>
<td>randomised trials</td>
<td>serious&lt;sup&gt;h&lt;/sup&gt;</td>
<td>not serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>not serious</td>
</tr>
<tr>
<td><strong>Use of prevention services (follow up: mean 6 months; assessed with: consistent condom use, self-reported, with casual or commercial male sex partner)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;g&lt;/sup&gt;</td>
<td>randomised trials</td>
<td>serious&lt;sup&gt;h&lt;/sup&gt;</td>
<td>not serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>not serious</td>
</tr>
<tr>
<td><strong>Use of prevention services (follow up: mean 6 months; assessed with: consistent condom use, self-reported, during receptive anal sex with male sex partner)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;g&lt;/sup&gt;</td>
<td>randomised trials</td>
<td>serious&lt;sup&gt;h&lt;/sup&gt;</td>
<td>not serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>not serious</td>
</tr>
<tr>
<td>Certainty assessment</td>
<td>Nº of patients</td>
<td>Effect</td>
<td>Certainty</td>
<td>Importance</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------</td>
<td>--------</td>
<td>-----------</td>
<td>------------</td>
</tr>
<tr>
<td>Nº of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>Use of prevention services (follow up: mean 6 months; assessed with: consistent condom use, self-reported, during insertive anal sex with male sex partner)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;3&lt;/sup,g</td>
<td>randomised trials</td>
<td>serious&lt;sup&gt;h&lt;/sup&gt;</td>
<td>not serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>not serious</td>
</tr>
<tr>
<td>Use of testing services (follow up: range 3 months to 6 months; assessed with: HIV testing)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2&lt;sup&gt;a&lt;/sup&gt;,&lt;sup&gt;e&lt;/sup&gt;,&lt;sup&gt;g&lt;/sup&gt;</td>
<td>randomised trials</td>
<td>serious&lt;sup&gt;h&lt;/sup&gt;</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Use of testing services (follow up: range 3 months to 12 months; assessed with: Syphilis testing)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>not serious</td>
</tr>
</tbody>
</table>

Cl: Confidence interval; RR: Risk ratio

**Explanations**

a. Study description: This serial cross-sectional study among MSM in the USA compared the number of MSM engaged in HIV/STI services through Grindr vs standard outreach methods.

b. Risk of bias (assessed through ROBINS-I): Potential bias due to confounding (two years separated the two data collection time periods, and through use of Grindr for outreach was the main intervention, the public health dept may have adjusted other methods of reaching out to potential HIV/STI service users). There was no denominator (population) to calculate rates; only number of contacts - which may have included duplicates. For the uptake of prevention/testing services outcome, no comparisons to pre-Grindr outreach were reported.

c. Inconsistency: This could not be evaluated, as there is only a single study.

d. Additional data: Non-comparative descriptive data after implementing Grindr outreach. Among the Grindr contacts, 68% remained engaged after the avatar identified as an outreach health educator. Of those contacts who remained engaged, 35% received some combination of counseling, referrals, testing, treatment, and/or followup. For engaged Grindr users who self-identified for testing encounters, 14 tested for HIV/gonorrhea/chlamydia (1 case of pharyngeal chlamydia, 2 cases of rectal chlamydia, 1 case of urogenital chlamydia, and 1 new HIV infection were identified) and 13 tested for syphilis (1 case of late latent syphilis was identified).

e. Study description: This stepped-wedge cluster RCT among 1381 MSM in China compared an integrated online HIV testing intervention (multimedia HIV testing campaign, online HIV testing service, and local testing promotion campaigns tailored for MSM) to conventional HIV testing programs routinely provided by local CDCs and CBOs.
f. Control (standard of care) risk based on baseline data from N=1318 participants in the Tang 2018 study.

g. Study description: This RCT among 100 MSM in China compared online HIV self-testing via WeTest (a private WeChat group which provided app-based messages and referrals to HIV services) and watching a brief video about self-administering the oral HIV self-test kit.

h. Risk of bias: Downgraded once for detection bias. Blinding was not possible given the nature of the intervention. Detection bias was possible as data was self-reported and may have been affected by a lack of blinding.

i. Imprecision: Downgraded because 95% CI for RR includes both 1 (no effect) AND either appreciable harm (0.75) or appreciable benefit (1.25). The study also had a small sample size (n<=50 in each arm) but we did not downgrade again for this.

j. Additional data: RR reported in GRADE table is the adjusted RR reported by study authors, accounting for group, time, age, education, income, occupation, and hukuo (Chinese household registration). We calculated the crude risk ratio (RR: 1.01, 95% CI: 0.60-1.72).

k. Additional data: RR reported in GRADE table is the adjusted RR reported by study authors, accounting for group, time, age, education, income, occupation, and hukuo (Chinese household registration). We calculated the crude risk ratio (RR: 1.09, 95% CI: 0.67-1.77).

l. Additional data: RR reported in GRADE table is the adjusted RR reported by study authors, accounting for group, time, age, education, income, occupation, and hukuo (Chinese household registration). We calculated the crude risk ratio (RR: 0.76, 95% CI: 0.41-1.41).

m. Additional data: RR reported in GRADE table is the adjusted RR reported by study authors, accounting for group, time, age, education, income, occupation, and hukuo (Chinese household registration). We calculated the crude risk ratio (RR: 1.00, 95% CI: 0.59-1.68).

n. Additional data: Tang et al. ran other analytical models (i.e. intervention effect assuming fixed secular trend, per protocol effect assuming fixed secular trend across clusters, intervention effect adjusted for province, intervention effect using multiple imputation) but all reported a relative risk between 1.43 and 1.49 and p<0.001. For meta-analysis, we chose to use the model adjusted for age, marital status and income. This study also reported the HIV testing in the past 3 months outcome disaggregated by age group (<=30 and >30 years old) and by in-person community activities (with and without).

o. Additional data: Zhu et al. also provided self-reported data for any oral HIV testing in the past 6 months (OR: 2.17, 95% CI: 1.08-4.37).

p. Control (standard of care) includes 1) events/participants from the Zhu 2019 study and 2) risk based on baseline data from N=1318 participants in the Tang 2018 study.

q. Imprecision: Downgraded because 95% CI for RR includes both 1 (no effect) AND either appreciable harm (0.75) or appreciable benefit (1.25).

References


### GRADE evidence profile for effectiveness review studies – Online case management

#### Use of prevention services (follow up: 6 months; assessed with: PrEP adherence (TFV-DP DBS concentrations ≥700 fmol/punch, equivalent to ≥4 doses of TDF/week))

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>randomised trials</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>none</td>
<td>36/73 (49.3%)</td>
<td>30/68 (44.1%)</td>
<td>RR 1.12 (0.78 to 1.59)</td>
<td>LOW</td>
</tr>
<tr>
<td></td>
<td></td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>none</td>
<td>36/73 (49.3%)</td>
<td>30/68 (44.1%)</td>
<td>RR 1.12 (0.78 to 1.59)</td>
<td>LOW</td>
</tr>
<tr>
<td></td>
<td></td>
<td>very serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>none</td>
<td>22/44 (50.0%)</td>
<td>19/47 (40.4%)</td>
<td>RR 1.24 (0.78 to 1.95)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td></td>
<td></td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>none</td>
<td>107/144 (74.3%)</td>
<td>64/94 (68.1%)</td>
<td>RR 1.09 (0.92 to 1.29)</td>
<td>LOW</td>
</tr>
<tr>
<td></td>
<td></td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>none</td>
<td>54/60 (90.0%)</td>
<td>45/60 (75.0%)</td>
<td>RR 1.20 (1.01 to 1.42)</td>
<td>LOW</td>
</tr>
</tbody>
</table>

#### Uptake of testing services (follow up: 8 months; assessed with: Repeat HIV testing (self-reported >1 test vs 0/1 test between baseline and followup assessment))

#### Treatment initiation (follow up: 90 days; assessed with: Linkage to care (completion of at least one HIV-related laboratory test (HIV viral load or CD4 count) within 90 days after release into the community))

#### Treatment initiation (follow up: 6 months; assessed with: Received primary HIV care within the last 6 months (self-reported))
### Certainty assessment

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Treatment retention/completion (follow up: range 4 months to 6 months; assessed with: ART adherence in the past 30 days)

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>№ of patients</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>randomised trials</td>
<td>serious⁹</td>
<td>not serious⁶</td>
<td>not serious</td>
<td>not serious</td>
<td>none</td>
<td>At the four-month (end of active intervention) timepoint, higher overall ART adherence in intervention than control (89.0% (95% CI: 83.4-94.6) intervention vs 77.2% (95% CI: 66.7-87.7) control, difference 11.8% (95% CI: 0.34-23.2), p=0.04). However, improvements in adherence were not sustained at the 6-month assessment (85.3% (95% CI: 80.0-90.6) intervention vs 89.0% (95% CI: 83.2-94.9) control, difference -3.7% (95% CI: -11.4-4.0), p=0.34).</td>
<td>1</td>
<td>50</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

### Treatment retention/completion (follow up: 6 months; assessed with: Engagement in HIV care (having seen an HIV care provider in the community at least once in the past 24 weeks))

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>randomised trials</td>
<td>serious⁶</td>
<td>not serious⁶</td>
<td>not serious</td>
<td>serious⁴</td>
<td>none</td>
<td></td>
<td>1</td>
<td>18 fewer per 1,000 (from 135 fewer to 108 more)</td>
</tr>
</tbody>
</table>

### Treatment retention/completion (follow up: 6 months; assessed with: Currently taking ART (self-reported))

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>observational studies</td>
<td>serious³</td>
<td>not serious⁵</td>
<td>not serious</td>
<td>serious⁴</td>
<td>none</td>
<td></td>
<td>1</td>
<td>133 more per 1,000 (from 21 fewer to 315 more)</td>
</tr>
</tbody>
</table>

### Viral load (follow up: 6 months; assessed with: Viral suppression (viral load < 200 copies/ml))

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>randomised trials</td>
<td>serious⁶</td>
<td>not serious⁶</td>
<td>not serious</td>
<td>serious⁴</td>
<td>none</td>
<td></td>
<td>1</td>
<td>17 fewer per 1,000 (from 180 fewer to 209 more)</td>
</tr>
</tbody>
</table>

### Viral load (assessed with: complete virologic suppression at any of the first 6 visits)

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>observational studies</td>
<td>serious³</td>
<td>not serious⁵</td>
<td>not serious</td>
<td>not serious</td>
<td>none</td>
<td></td>
<td>1</td>
<td>315 more per 1,000 (from 255 more to 380 more)</td>
</tr>
</tbody>
</table>
### Certainty assessment

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Number of patients</th>
<th>Effect</th>
<th>Absolute (95% CI)</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1^L</td>
<td>observational studies</td>
<td>serious^m</td>
<td>not serious^c</td>
<td>not serious^d</td>
<td>none</td>
<td>online case management, standard of care</td>
<td>37/54 (68.5%)</td>
<td>RR 1.05</td>
<td>33 more per 1,000 (from 137 fewer to 260 more)</td>
<td>LOW</td>
<td>critical</td>
</tr>
</tbody>
</table>

#### Viral load (follow up: 6 months; assessed with: Viral suppression (viral load < 200 copies/ml, self-reported))

**Explanations**

a. Study description: This RCT among 200 HIV-15-19yo MSM and TG women in Thailand compared using a mobile app with youth friendly services AND PrEP self-assessment, rewards, and appointment reminders with a mobile app with youth friendly services only.

b. Risk of bias: Downgraded once because some concerns of bias. Details of the randomisation and/or allocation process are not documented. No additional information on allocation concealment; some baseline differences between groups in terms of sociodemographics and outcome measures at baseline suggest potential issues.

c. Inconsistency: This could not be evaluated, as there is only a single study.

d. Imprecision: Downgraded once because 95% CI for RR includes both 1 (no effect) AND either appreciable harm (0.75) or appreciable benefit (1.25). Small sample size in both arms (but did not downgrade again).

e. Additional data: Songtaweesin et al. reported aOR: 1.18 (95% CI: 0.58-2.42) adjusted for gender identity, age, number of sex partners, and self-perceived risk for HIV infection. Authors also presented data for the 3mo timepoint: 44/81 (54.3%) intervention vs 40/79 (50.6%) control, RR 1.07 (95% CI: 0.80-1.44), aOR 1.08 (95% CI: 0.54-2.16).

f. Study description: This RCT among 113 HIV- MSM in the USA compared using a mobile app (Status Update Project) with a monthly My Health Survey to recommend next HIV test date, prevention 411 with HIV/STI information, etc to no treatment.

g. Risk of bias: Downgraded twice because of high risk of bias (some concerns across multiple domains). Details of the randomisation and/or allocation process are not documented. No additional information on allocation concealment; some baseline differences between groups in terms of sociodemographics and outcome measures at baseline suggest potential issues. By 8-month follow-up, loss-to-follow-up rate was 21% in the intervention arm and 12% in the control arm; differences in missingness could depend on the true value but we judged it unlikely. Given the intervention of interest (online case mgmt.), blinding was not possible for participants and personnel. Deviations from the intended intervention due to lack of blinding were not documented. We judged that self-reported outcomes (with no validation from lab/other measures) were potentially influenced by lack of blinding (potential detection bias).

h. Additional data: Horvath et al. reported data at the 4month followup assessment as well: 8/47 (17.0%) intervention vs 2/52 (3.8%) control, RR: 4.4 (95% CI: 0.9-19.8), aRR 3.4 (95% CI: 0.7-15.6) adjusting for demographic, behavioral, and HIV testing intention and behavior variables.

i. Study description: This cohort study among 238 HIV+ adults soon to be released from prison in the USA compared an online tailored personalized website for HIV/STI testing to access to an online provider directory webpage only.

j. Risk of bias: Cohort study assessed with ROBINS-I. Baseline and time-varying confounding was not adjusted for by the variables available in the study. Selection of participants into the study was not based on participant characteristics observed after the start of the intervention, but the start of follow-up and start of intervention did not coincide for most participants (intervention group was those who successfully received the case management video conference in time for their release from prison; control group was those who did not receive the video conference in time).

k. Additional data: Brantley et al. reported aOR 1.2 (95% CI: 0.6-2.3), adjusting for race, birth sex, age, HIV transmission risk, time since HIV diagnosis, AIDS diagnosis history, baseline (pre-release) viral suppression status, HIV diagnosis status prior to incarceration, and HIV care engagement status prior to incarceration.
l. Study description: This cohort study among 120 HIV+ 18-34yo MSM and TG women in the USA compared those who completed a 6-month digital HIV care navigation (text messaging with personal HIV care navigator) to those who did not complete the 6 month intervention.

m. Risk of bias: Cohort study assessed using ROBINS-I. Baseline and time-varying confounding was not adjusted for by the variables available in the study. Among the 120 participants enrolled in the intervention, 60 were lost to follow up and did not complete the intervention. The 60 who completed the intervention were considered the intervention group, and the 60 who were lost to follow up (67% for unknown reasons, 10% for phone loss, 15% for moving out of jurisdiction, and other reasons) were considered the control group. However, characteristics of the control group were not different from the overall sample (or the intervention group). Given the intervention of interest (online case mgmt.), blinding was not possible for participants and personnel and outcome was self-reported.

n. Imprecision: Downgraded once because small sample size in both arms.

o. Study description: This RCT among 90 HIV+ stimulant using MSM in the USA compared using a mobile app (APP+) with IMB HIV/ART content, a choose your own adventure story, and medication self-monitoring to no treatment.

p. Risk of bias: Given the intervention of interest (online case mgmt.), blinding was not possible for participants and personnel. However, deviations from the intended intervention due to lack of blinding were not documented, and any potential deviations were unlikely to have affected the outcome. We judged that self-reported outcomes (with no validation from lab/other measures) were potentially influenced by lack of blinding (detection bias).

q. Additional data: Horvath et al. reported no significant differences at any assessment timepoints between intervention and control for other measurements of ART adherence: taking ART within 2 hours of the scheduled time, adherence while using stimulants, taking ART within 2 hours of the scheduled time while using stimulants, almost always or always (vs never, rarely, sometimes, or usually) taking ART doses correctly in the past 30 days.

r. Study description: This RCT among 110 HIV+ adults soon to be or recently released from prison in the USA compared the CARE+Corrections intervention (computerized motivational interview and individual risk reduction plan pre-release plus text messaging about care navigation post-release) to an attention-control (opioid overdose prevention video and HIV providers/resources printout).

s. Additional data: Kuo et al. present aOR 2.04 (95% CI: 0.62-6.70), adjusting for the location of study enrollment, gender, sexual orientation, depressive symptomatology, and positive PTSD score.

t. Additional data: Kuo et al. present aOR 2.04 (95% CI: 0.62-6.70), adjusting for the location of study enrollment, gender, sexual orientation, depressive symptomatology, and positive PTSD score.

u. Study description: This cohort study among 1201 HIV+ prisoners in the USA compared those using telemedicine for HIV care to on-site management by correctional facility physicians.

v. Risk of bias: Cohort study assessed with ROBINS-I. Downgraded once for moderate concerns in one risk of bias domain. Baseline and time-varying confounding was not adjusted for by the variables available in the study.

w. Additional data: Horvath et al. reported no significant differences at any assessment timepoints between intervention and control for other measurements of ART adherence: taking ART within 2 hours of the scheduled time, adherence while using stimulants, taking ART within 2 hours of the scheduled time while using stimulants, almost always or always (vs never, rarely, sometimes, or usually) taking ART doses correctly in the past 30 days.

x. Study description: This cohort study among 1201 HIV+ prisoners in the USA compared those using telemedicine for HIV care to on-site management by correctional facility physicians.

y. Imprecision: Downgraded once because small sample size in both arms.

z. Study description: This RCT among 90 HIV+ stimulant using MSM in the USA compared using a mobile app (APP+) with IMB HIV/ART content, a choose your own adventure story, and medication self-monitoring to no treatment.

References


### GRADE evidence profile

**Table 4. GRADE evidence profile for effectiveness review studies - Targeted online health information**

<table>
<thead>
<tr>
<th>Nº of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Nº of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Use of prevention services (follow up: 30 days; assessed with: Vaccination for hepatitis A or B, HPV, or meningococcal meningitis)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,2</td>
<td>randomised trials</td>
<td>serious</td>
<td>not serious</td>
<td>serious</td>
<td>serious</td>
<td>none</td>
<td>0/68 (0.0%)</td>
<td>0/36 (0.0%)</td>
<td>not estimable</td>
<td></td>
</tr>
<tr>
<td><strong>Uptake of testing services for HIV/VH/STIs (follow up: 12 weeks; assessed with: Followed up for HIV test result (after requesting and returning HIV test kit))</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,2</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>serious</td>
<td>none</td>
<td>8/57 (14.0%)</td>
<td>0/55 (0.9%)</td>
<td>RR 3.56 (0.32 to 39.65)</td>
<td>23 more per 1,000 (from 6 fewer to 351 more)</td>
</tr>
<tr>
<td><strong>Uptake of testing services for HIV/VH/STIs (follow up: 30 days; assessed with: Tested for HIV or STIs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,2</td>
<td>randomised trials</td>
<td>serious</td>
<td>not serious</td>
<td>serious</td>
<td>serious</td>
<td>none</td>
<td>22/68 (32.4%)</td>
<td>8/36 (22.2%)</td>
<td>RR 1.46 (0.72 to 2.94)</td>
<td>102 more per 1,000 (from 62 fewer to 431 more)</td>
</tr>
<tr>
<td><strong>Uptake of testing services for HIV/VH/STIs (follow up: 30 days; assessed with: HIV testing among those who tested for any HIV/STIs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,2</td>
<td>randomised trials</td>
<td>very serious</td>
<td>not serious</td>
<td>serious</td>
<td>very serious</td>
<td>none</td>
<td>18/22 (81.8%)</td>
<td>6/8 (75.0%)</td>
<td>RR 1.09 (0.70 to 1.70)</td>
<td>68 more per 1,000 (from 225 fewer to 525 more)</td>
</tr>
<tr>
<td><strong>Uptake of testing services for HIV/VH/STIs (follow up: 30 days; assessed with: Gonorrhea testing among those who tested for any HIV/STIs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,2</td>
<td>randomised trials</td>
<td>very serious</td>
<td>not serious</td>
<td>serious</td>
<td>very serious</td>
<td>none</td>
<td>9/22 (40.9%)</td>
<td>2/8 (25.0%)</td>
<td>RR 1.64 (0.45 to 6.01)</td>
<td>160 more per 1,000 (from 138 fewer to 1,000 more)</td>
</tr>
<tr>
<td>Nº of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
<td>Other considerations</td>
<td>Nº of patients</td>
<td>Effect</td>
<td>Certainty</td>
<td>Importance</td>
</tr>
<tr>
<td>---------------</td>
<td>--------------</td>
<td>--------------</td>
<td>---------------</td>
<td>--------------</td>
<td>-------------</td>
<td>---------------------</td>
<td>----------------</td>
<td>--------</td>
<td>-----------</td>
<td>------------</td>
</tr>
<tr>
<td><strong>Uptake of testing services for HIV/VH/STIs (follow up: 30 days; assessed with: Chlamydia testing among those who tested for any HIV/STIs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,a</td>
<td>randomised trials</td>
<td>very serious</td>
<td>not serious</td>
<td>serious</td>
<td>very serious</td>
<td>none</td>
<td>12/22 (54.5%)</td>
<td>2/8 (25.0%)</td>
<td>RR 2.18 (0.62 to 7.69)</td>
<td>295 more per 1,000 (from 95 fewer to 1,000 more)</td>
</tr>
<tr>
<td><strong>Uptake of testing services for HIV/VH/STIs (follow up: 30 days; assessed with: Syphilis testing among those who tested for any HIV/STIs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,a</td>
<td>randomised trials</td>
<td>very serious</td>
<td>not serious</td>
<td>serious</td>
<td>very serious</td>
<td>none</td>
<td>14/22 (63.6%)</td>
<td>2/8 (25.0%)</td>
<td>RR 2.55 (0.74 to 8.81)</td>
<td>387 more per 1,000 (from 65 fewer to 1,000 more)</td>
</tr>
<tr>
<td><strong>Uptake of testing services for HIV/VH/STIs (follow up: 30 days; assessed with: Anal pap smear among those who tested for any HIV/STIs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,a</td>
<td>randomised trials</td>
<td>very serious</td>
<td>not serious</td>
<td>serious</td>
<td>very serious</td>
<td>none</td>
<td>1/22 (4.5%)</td>
<td>1/8 (12.5%)</td>
<td>RR 0.36 (0.03 to 5.15)</td>
<td>80 fewer per 1,000 (from 121 fewer to 519 more)</td>
</tr>
<tr>
<td><strong>Use of testing services for HIV/VH/STIs (follow up: 7 weeks; assessed with: Syphilis testing)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,m</td>
<td>observational studies</td>
<td>serious</td>
<td>not serious</td>
<td>serious</td>
<td>not serious</td>
<td>none</td>
<td>2025/-</td>
<td>2049/-</td>
<td>Rate ratio 1.00 (0.94 to 1.07)</td>
<td>-- per 1000 patient(s) per years (from -- to --)</td>
</tr>
</tbody>
</table>

CI: Confidence interval; RR: Risk ratio

**Explanations**

a. Study description: This RCT among 130 MSM in USA compared a tailored website (including content customized to the user based on prior testing experiences and motivations, barriers and resources to testing, and important values - information gathered about each study participant during baseline measurement) to access to an online provider directory with no tailored content. N=86 were allocated to the intervention arm and n=44 to the control.

b. Risk of bias: Downgraded once for detection bias. Blinding was not possible given the nature of the intervention. Detection bias was possible as data was self-reported and may have been affected by a lack of blinding. Also, no information on randomization/allocation methods was reported (appears to be 2:1 allocation to the intervention:control).

c. Inconsistency: This could not be evaluated, as there is only a single study.

d. Indirectness: Downgraded once because intervention was not exactly “targeted health information.” Intervention was an online health intervention (Get Connected! website) tailored to study participants based on sociodemographic/behavioral/motivational information, but this intervention was not exactly “targeted health information” per se because the information used for tailoring was collected through the study’s baseline assessment.
e. Imprecision: Downgraded because no events and low sample size in both arms.

f. Study description: This RCT among 112 MSM in USA compared using social networks/peer leaders on Facebook delivering HIV information in group settings and individually (via chat, wall posts, and personal messages) to peer leaders on Facebook delivering general health information.

g. Indirectness: Downgraded once because intervention was not exactly “targeted health information.” Intervention was a social networking intervention with peer leaders on Facebook in study-created groups of 12 to disseminate health information to their group members through sending chat messages and wall posts (general conversation and HIV prevention/testing information, tailored to participant response/engagement), not exactly “targeted health information.”

h. Imprecision: Downgraded because no event in control arm and low sample size in both arms. RR calculated using continuity correction of 0.5; study authors reported number of events and percentages per arm only, with no statistical analyses.

i. Additional data: The study also reports outcomes that are precursors to the outcome we present in the GRADE table (followed up to receive HIV test result). The study reported that 25/57 (44%) in the intervention arm requested a HIV test kit, compared to 11/55 (20%) in the control arm (RR: 2.19, 95% CI: 1.20-4.01). Of those who requested a HIV test kit, 9 in the intervention arm returned the HIV test kit (9/25, 36%) compared to 2 in the control arm (2/11, 18%) (RR: 1.98, 95% CI: 0.51-7.70).

j. Imprecision: Downgraded because 95% CI for RR includes both 1 (no effect) AND either appreciable harm (0.75) or appreciable benefit (1.25). The study also had a small sample size (n<=50 in each arm) but we did not downgrade again for this.

k. Risk of bias: Downgraded twice: 1) for detection bias, as blinding was not possible given the nature of the intervention. Detection bias was possible as data was self-reported and may have been affected by a lack of blinding. 2) because this was a sub-group of the “uptake of testing for HIV/STIs” above so the intervention and control groups were not randomized per se.

l. Imprecision: Downgraded twice, 1) because 95% CI for RR includes both 1 (no effect) AND either appreciable harm (0.75) or appreciable benefit (1.25), and 2) this is a subgroup of the row above so a very small sample size (n=22 in the intervention arm and n=8 in the control).

m. Study description: This serial cross-sectional study among MSM in Canada compared the number of syphilis tests ordered (public health laboratory data) in the 7 weeks prior to the launch of the ad campaign to the number of tests ordered in the 7 weeks after the first ads appeared.

n. Risk of bias: The study authors used multivariable Poisson regression to calculate the rate ratio of syphilis testing frequency, post-period compared to pre-period, but provided no information on how they calculated rates from pure “number of tests in each period” data nor on what variables they used in their multivariable regression.

o. Indirectness: Downgraded once because the intervention was not exactly “targeted health information”. Intervention was a social media syphilis testing campaign, where ads were hosted on four online media platforms: Grindr, Facebook, Squirt and the Gay Ad Network. When clicked, ads would direct the user to an information website on the syphilis outbreak and the importance of testing. Ads were targeted in that they were geo-tagged for location and the specific media platforms had specific target populations (clients) but otherwise not exactly “targeted health information”.

References


Peer navigation

Do peer navigators improve initiation and retention in HIV/VH/STI treatment programmes for people from key populations?

Systematic review team: Caitlin Kennedy and Teresa Yeh, Johns Hopkins University

Background

Peer navigation is rooted in the concept of patient navigation, where vulnerable patients are directly assisted to help find their way through complex health care systems to obtain timely diagnosis and treatment. Instead of formal health workers, lay staff members who could be considered peers of the participants and could promote trust among the population fill this role (Cunningham et al., 2018). Peer navigators are often employed at community-based services, primary health care settings, and testing and treatment facilities that are designed to serve people from key population groups (KP). Their role is to support KP after screening positive to access confirmatory diagnosis, treatment services and to support the early stage of treatment with regular peer support as well as accompanying KP to appointments, supporting navigation to other related health services, etc. While widely employed in KP-related health services, there are no recommendations about their effectiveness in increasing uptake of treatment initiation and retention for key populations.

Previous trials among general (not key) populations have shown promise for peer navigation for HIV/VH/STIs, but not consistently across all outcomes. In the United States, a randomized controlled trial (RCT) on peer navigators for HIV demonstrated improved retention in HIV, but did not show significant effects on viral suppression at 12 months (Cabral et al., 2018). In the United Kingdom, an RCT on peer navigators for hepatitis C virus (HCV) improved engagement in care (Stagg et al., 2019). In Canada, an RCT on peer navigators for HCV showed they successfully reached marginalized individuals and increased HCV knowledge, but did not improve linkage to HCV care after diagnosis (Broad et al., 2020). In Georgia, a pilot study demonstrated that a simple peer-support intervention resulted in high treatment uptake and retention among PWID (Kikvidze et al., 2018).

Currently, WHO has no prior recommendations specifically on peer navigation for HIV/VH/STI services among KP. However, there exist several related recommendations. The 2017 WHO Guidelines on Hepatitis B and C testing gave a conditional recommendation that evidence-based interventions like “peer and lay health worker support in community-based settings (moderate certainty) […] should be considered to promote uptake of hepatitis testing and linkage to care and treatment initiation” (WHO, 2017). The 2021 WHO Consolidated Guidelines on HIV prevention, testing, treatment, service delivery and monitoring gave a strong recommendation that “[f]ollowing an HIV diagnosis, a package of support interventions should be offered to ensure timely linkage to care for all people living with HIV” including such interventions as “peer support and navigation approaches for linkage” where peer support included peer counseling (WHO, 2021).

Methods

We conducted a systematic review of the evidence in three related areas: effectiveness of the intervention, values and preferences of clients and health workers related to the intervention, and costs or cost-effectiveness of the intervention.

Effectiveness review

The effectiveness review was designed according to the PICO form as follows: Do peer navigators improve initiation and retention in HIV/viral hepatitis (VH)/sexually transmitted infection (STI) treatment programmes for people from key populations?
Populations: Men who have sex with men (MSM), sex workers (SW), people who inject drugs (PWID), trans and gender diverse individuals (TGD), and prisoners or people in closed settings (PRIS)

Interventions: Peer navigation for HIV/VH/STI treatment programs. We did not include interventions using peer navigators for PrEP, peer navigators for HIV testing, peer education, or peer referral only.

Comparator: No peer navigation

Outcomes:
1. Time to diagnosis (time between initial positive test result and confirmatory diagnosis) or linkage to care (time between initial positive test result and engagement in HIV/VH/STI care and treatment services)
2. Treatment initiation for HIV/VH/STIs
3. Treatment retention/completion for HIV/VH/STIs
4. Viral load (e.g. HIV, HCV)
5. Cure (for HCV and bacterial STIs, e.g. syphilis, gonorrhoea)
6. Mortality

Inclusion criteria for this review were as follows:
1. Study design: RCTs or observational studies that compared the intervention vs. the comparison
2. Measured one or more of the outcomes of interest
3. Published in a peer-reviewed journal from January 1, 2010 through the search date of May 27, 2021

No restrictions were placed based on location of the intervention or language of the publication.

We searched four databases (CINAHL, PsycINFO, PubMed, and EMBASE) for relevant peer-reviewed publications. Search terms covered terms for key populations, infections (HIV, VH, STIs), and peer navigator interventions. The full search strategy for PubMed is available in the Appendix; this was adapted to other databases. This search was complemented by several other ways of identifying articles. First, we ran two earlier searches for behavioural interventions for key populations more broadly – one in 2019 as part of an original scoping review, and one in March 2020 as part of a search just for RCTs. Articles identified through these prior searches were included in the review. Second, we hand-searched the references of articles identified for inclusion in the review. Third, we contacted experts in the field (including GDG members) to identify any additional articles we may have missed.

Titles, abstracts, citation information, and descriptor terms of citations identified through the search strategy were screened for initial inclusion. Full text articles were obtained of all selected abstracts and two independent reviewers assessed all full-text articles for eligibility to determine final study selection. Differences were resolved through consensus. Data were extracted independently by two reviewers using standardized data extraction forms in Excel. Differences in data extraction were resolved through consensus and referral to a senior study team member when necessary.

The following information was gathered from each included study in the effectiveness review:
- citation information (author, year, title, journal, language of article)
- location (country, urban/rural, World Bank income classification, WHO region)
- key population (MSM, PWID, SW, TGD, PRIS) and description (gender, age, chemsex activity)
- sample size (n)
- study design (specific study design; RCT vs observational; follow-up periods and loss to follow-up)
- intervention summary and longer description (including who delivered intervention, where intervention was provided, how long/frequent intervention was)
- comparator description
- study outcomes (based on PICO's above)
- study outcomes (analytic approach, outcome measures/definitions, intervention vs comparison group, n/% or effect sizes with confidence intervals or significance levels, conclusions, limitations)

We contacted study authors in several cases where full information was not available from the published articles.

For randomized trials, risk of bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias. Methodological components of the studies were assessed and classified as high or low risk of bias. For studies that are not randomized trials but were comparative, study rigor was assessed using the Evidence Project 8-item checklist for intervention evaluations and ROBINS-I.

Data were analysed according to coding categories and outcomes. Where there were multiple studies reporting the same outcome for the same intervention-comparator comparison for the same population, we planned to conduct meta-analysis. All outcomes were stratified and presented by key population – MSM, SW, PWID, TGD, and PRIS. Findings were summarized in GRADE Evidence Profile tables using GRADEPro.

Values and preferences review
The same search terms were used to search and screen for studies to be included in the values and preferences review. Studies were included in this review if they presented primary data examining the values and preferences of potential beneficiaries, communities, providers, and stakeholders for peer navigator interventions. These studies could be qualitative or quantitative in nature, but had to present primary data collection – think pieces and review articles were not included. Values and preferences literature was summarized qualitatively and was organized by study design and methodology, location, and population.

Cost and resource needs
The same search terms were used to search and screen for studies to be included in the cost review. Studies were included in this review if they presented primary data comparing costing, cost-effectiveness, cost-utility, or cost-benefit of the intervention and comparison listed in the PICO question above, or if they presented cost-effectiveness of the intervention as it relates to the PICO outcomes listed above. We planned to summarize cost literature summarized qualitatively. We planned to organize cost literature into four categories (health sector costs, other sector costs, patient/family costs, and productivity impacts) and within each category present it by study design/methodology, location, and population.

Findings are presented separated by effectiveness, values and preferences, and cost reviews.

Results
Figure 2 presents the flow chart showing inclusion of articles in the systematic review. We identified 4 articles meeting the inclusion criteria for the effectiveness review, 2 for values and preferences, and 0 for costs.
Figure 2. Flow chart showing inclusion of articles across the stages of the systematic review

Effectiveness review

Overall, four studies met the inclusion criteria for the effectiveness review (Cunningham et al., 2018; Kerrigan et al., 2019; Kerrigan et al., 2016, and Reback et al., 2019). Table 2 provides a description of studies included in the effectiveness review. All studies focused on HIV. There were two RCTs and two observational studies (one before/after study and one cross-sectional dose–response analysis of a one-arm study). Two studies were conducted in the United States, one with prisoners (including 15% transgender individuals) and one with transgender individuals. The other two studies were conducted in with sex workers in the Dominican Republic and Tanzania. The study with prisoners focused on peer navigation for transition out of prison. The two studies with sex workers included multi-component, community empowerment interventions that also included a peer navigation component. Finally, the study with transgender individuals included continency management (payment for achievement of target behaviors/goals) as well as peer navigation.
Table 2. Description of studies included in the effectiveness review

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Study design</th>
<th>Population</th>
<th>Disease focus</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cunningham et al., 2018</td>
<td>USA</td>
<td>RCT</td>
<td>PRIS (15% TG)</td>
<td>HIV</td>
<td>Peer navigation for transition out of prison</td>
<td>Standard of care</td>
<td>Time to linkage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Retention</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Viral load</td>
</tr>
<tr>
<td>Kerrigan et al., 2016</td>
<td>Dominican Republic</td>
<td>Before/after</td>
<td>SW</td>
<td>HIV</td>
<td>Multi-component intervention, including peer navigators to ensure access to and retention in HIV care services and social support</td>
<td>Standard of care</td>
<td>Retention</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Viral load</td>
</tr>
<tr>
<td>Kerrigan et al., 2019</td>
<td>Tanzania</td>
<td>RCT</td>
<td>SW</td>
<td>HIV</td>
<td>Multi-component intervention, including peer navigators to navigate HIV care services</td>
<td>Standard of care</td>
<td>Time to linkage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Retention</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Viral load</td>
</tr>
<tr>
<td>Reback et al., 2019</td>
<td>USA</td>
<td>Cross-sectional dose-response analysis of a one-arm study</td>
<td>TG</td>
<td>HIV</td>
<td>Peer navigation and contingency management (CM) (more sessions attended)</td>
<td>Fewer sessions attended</td>
<td>Retention</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Viral load</td>
</tr>
</tbody>
</table>

Table 3 presents the risk of bias assessments for these studies. The two RCTs were rated low for overall risk of bias. While Cunningham et al. (2018) had high loss to follow-up, it was similar in both arms. Kerrigan et al. (2019) rated moderate for risk of bias in measurement of the outcome as some outcomes were self-report. Similarly, both observational studies had low risk of bias overall. Kerrigan et al. (2016) rated moderate for risk of bias in measurement of the outcome as some outcomes were self-report. Reback et al. (2019) was rated as high risk of bias due to missing data as there was high attrition in the study over time.

Table 4 presents the GRADE evidence profile for all outcomes. The RCTs provided data for three of our PICO outcomes: 1. Time to diagnosis (time between initial positive test result and confirmatory diagnosis) or linkage to care (time between initial positive test result and engagement in HIV/VH/STI care and treatment services), 3. Treatment retention/completion for HIV/VH/STIs, and 4. Viral load (e.g. HIV, HCV). The observational studies measured the same outcomes.

No studies measured our other outcomes: treatment initiation for HIV/VH/STIs, cure (for curable STIs, e.g. HCV, syphilis, gonorrhoea), or mortality.

Three studies measured time to diagnosis or linkage to care. One RCT with high certainty showed peer navigators made no difference in probability of HIV care visits after jail release among prisoners in the USA. A low certainty RCT among sex workers in Tanzania showed peer navigators improved ever linkage to HIV care. The moderate certainty observational study of contingency management and peer educators showed improvements in having a first HIV care visit.
### Table 3. Risk of bias assessments: Cochrane tool (for RCTs) and ROBINS-I (for observational studies)

#### Cochrane Risk of Bias Tool (for RCTs)

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Risk of bias arising from the randomization process</th>
<th>Risk of bias due to deviations from the intended interventions</th>
<th>Risk of bias due to missing outcome data</th>
<th>Risk of bias in measurement of the outcome</th>
<th>Risk of bias in selection of the reported result</th>
<th>Overall risk of bias judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cunningham et al., 2018</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Kerrigan et al., 2019</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

#### ROBINS-I Tools (for non-RCTs)

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Bias due to confounding</th>
<th>Bias in selection of participants into the study</th>
<th>Bias in classification of interventions</th>
<th>Bias due to deviations from intended intervention</th>
<th>Bias due to missing data</th>
<th>Bias in measurement of outcomes</th>
<th>Bias in selection of the reported result</th>
<th>Overall risk of bias judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kerrigan et al., 2016</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>No information</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
<td>Low risk of bias</td>
</tr>
<tr>
<td>Reback et al., 2019</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low risk of bias</td>
</tr>
</tbody>
</table>

1. Loss to follow-up of approximately 70% in both arms, but similar reasons in both arms.
2. Some outcomes are self-reported
3. High attrition

For treatment retention/completion, all three studies measuring this outcome reported current ART use. The RCT among prisoners in the USA showed no difference in ART use with peer navigators (moderate certainty), while the RCT and before/after study with sex workers both showed modest improvements in ART use (low certainty). All four studies measured viral load (high to moderate certainty). The RCT among prisoners in the USA and the contingency management study with TGD individuals in the USA both showed a positive impact of peer navigators on viral load (high to moderate certainty). The RCT and observational study among SW in the Dominican Republic and Tanzania both showed no difference in viral load (moderate certainty).
### GRADE evidence profile

**GRADE evidence profile for effectiveness review studies – Peer navigation**

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>No of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>peer navigation</td>
<td>no peer navigation</td>
<td>Relative (95% CI)</td>
<td>Absolute (95% CI)</td>
</tr>
<tr>
<td>Time to diagnosis or linkage to care (follow up: mean 12 months; assessed with: probability of HIV primary care visits after jail release)</td>
<td>1.1,a</td>
<td>randomised trials</td>
<td>not serious b</td>
<td>not serious c</td>
<td>not serious</td>
<td>not serious</td>
<td>none</td>
<td>82/117 (70.1%)</td>
<td>87/118 (73.7%)</td>
<td>RR 0.95 (0.81 to 1.12)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to diagnosis or linkage to care (follow up: mean 10 months; assessed with: ever linked to HIV care)</td>
<td>1.2.f</td>
<td>randomised trials</td>
<td>serious f</td>
<td>not serious c</td>
<td>serious h</td>
<td>not serious</td>
<td>none</td>
<td>72/91 (79.1%)</td>
<td>44/80 (55.0%)</td>
<td>RR 1.44 (1.15 to 1.80)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to diagnosis or linkage to care (assessed with: first HIV care visit)</td>
<td>1.3.j</td>
<td>observational studies</td>
<td>not serious b</td>
<td>not serious c</td>
<td>serious k</td>
<td>not serious</td>
<td>none</td>
<td>Regression coefficient 0.38 (0.09 to 0.67)</td>
<td>-- per 1,000 (from -- to --)</td>
<td>⭐⭐⭐⭐⭐</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment retention/completion for HIV/VH/STIs (follow up: mean 12 months; assessed with: current ART use)</td>
<td>1.1,a</td>
<td>randomised trials</td>
<td>serious f</td>
<td>not serious c</td>
<td>not serious</td>
<td>not serious</td>
<td>none</td>
<td>104/125 (83.2%)</td>
<td>107/125 (85.6%)</td>
<td>RR 0.97 (0.87 to 1.08)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment retention/completion for HIV/VH/STIs (follow up: mean 18 months; assessed with: current ART use)</td>
<td>1.2.f</td>
<td>randomised trials</td>
<td>serious f</td>
<td>not serious c</td>
<td>serious h</td>
<td>not serious</td>
<td>none</td>
<td>74/91 (81.3%)</td>
<td>51/80 (63.7%)</td>
<td>RR 1.28 (1.05 to 1.55)</td>
</tr>
</tbody>
</table>

---

1. a, b, c, d, e, f, g, h, i, j, k, l, m, n, o, p, q, r, s, t, u, v, w, x, y, z
## Treatment retention/completion for HIV/VH/STIs (follow up: mean 10 months; assessed with: current ART use)

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>№ of patients</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a,n&lt;/sup&gt;</td>
<td>observational studies</td>
<td>serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>not serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>not serious</td>
<td>none</td>
<td>178/228 (78.1%)</td>
<td>RR 1.11 (1.03 to 1.19)</td>
</tr>
</tbody>
</table>

## Viral load (follow up: mean 12 months; assessed with: HIV viral suppression: undetectable viral load (<75 copies/mL))

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>№ of patients</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>randomised trials</td>
<td>not serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>not serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>not serious</td>
<td>not serious</td>
<td>none</td>
<td>62/125 (49.6%)</td>
<td>RR 1.38 (1.03 to 1.85)</td>
</tr>
</tbody>
</table>

## Viral load (follow up: mean 12 months; assessed with: HIV viral suppression (<400 copies/mL))

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>№ of patients</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;j&lt;/sup&gt;</td>
<td>randomised trials</td>
<td>not serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>not serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>serious&lt;sup&gt;b&lt;/sup&gt;</td>
<td>not serious</td>
<td>none</td>
<td>46/91 (50.5%)</td>
<td>RR 1.07 (0.78 to 1.46)</td>
</tr>
</tbody>
</table>

## Viral load (follow up: mean 10 months; assessed with: HIV detectable viral load (>50 copies/ml))

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>№ of patients</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;n&lt;/sup&gt;</td>
<td>observational studies</td>
<td>not serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>not serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>not serious</td>
<td>none</td>
<td>116/228 (50.9%)</td>
<td>RR 1.02 (0.93 to 1.12)</td>
</tr>
</tbody>
</table>

## Viral load (assessed with: HIV undetectable viral load (<20-75 copies/mL))

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>№ of patients</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;j&lt;/sup&gt;</td>
<td>observational studies</td>
<td>not serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>not serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>serious&lt;sup&gt;x&lt;/sup&gt;</td>
<td>not serious</td>
<td>none</td>
<td>Regression coefficient 0.10 (0.05 to 0.14)</td>
<td>-- per 1,000 (from -- to --)</td>
</tr>
</tbody>
</table>

---

**Certainty assessment**

<table>
<thead>
<tr>
<th>№ of patients</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>peer navigation</td>
<td>no peer navigation</td>
</tr>
<tr>
<td>Relative (95% CI)</td>
<td>Absolute (95% CI)</td>
</tr>
</tbody>
</table>

**Explanations**

- Study description: This RCT among 356 PRIS (including 15% TG) living with HIV in USA compared peer navigation for transition out of prison to standard of care.
b. Risk of bias: Not downgraded for detection bias. Blinding was not possible given the nature of the intervention. Detection bias was unlikely as participant-reported visit data was validated by comparison with electronic visit records.

c. Inconsistency: This could not be evaluated, as there is only a single study.

d. Additional time points: Linkage to HIV primary care after jail release. 3 month follow-up (n=312): Intervention: 101/156, Control: 99/156, RR: 1.02 (0.86 to 1.20), probability difference: 0.01 (-0.09 to 0.12, p=0.81). 6 month follow-up (n=260): Intervention: 93/128, Control: 82/128, RR: 1.23 (1.02 to 1.48), probability difference: 0.12 (0.04 to 0.22, p=0.01).

e. Number of patients data provided through communication with study authors. RR calculated directly from these data. At 12 month follow-up, the authors reported only a probability difference of 0.04 (-0.04 to 0.12) calculated from an intervention probability of 0.92 (0.87 to 0.97) and control probability of 0.88 (0.82 to 0.94).

f. Study description: This RCT among 171 SW living with HIV in Tanzania compared a multi-component intervention, including peer navigators to navigate HIV care services, to standard of care.

g. Risk of bias: Downgraded once for detection bias. Blinding was not possible given the nature of the intervention. Detection bias was possible as data was self-reported and may have been affected by a lack of blinding.

h. Indirectness: Downgraded because intervention was multi-component and included a community-led drop-in center with mobilization activities, sensitivity training for HIV clinical providers and police, venue-based peer-education and condom distribution, and text messages and reminders to promote solidarity and care engagement, in addition to peer navigation.

i. Regression coefficient for estimated associations between attendance to peer navigation sessions and achievement of continency management target (first HIV care visit), using a partial proportional odds ordinal logistic regression.

j. Study description: This cross-sectional dose-response analysis of a one-arm study among 139 TG living with HIV in USA provided peer navigation and contingency management (payment for achieving care milestones and compared those who attended fewer sessions to those who attended more sessions.

k. Indirectness: Downgraded because intervention included contingency management in addition to peer navigation.

l. Number of patients not reported. Effect: probability difference calculated from intervention probability: 0.92 (0.87 to 0.97), control probability: 0.88 (0.82 to 0.94)

m. RR calculated based on number of patients data. Study authors reported a probability difference of 0.18 (0.02 to 0.40). Additional time points: ART use. 3 month follow-up (n=315): probability difference: -0.01 (-0.06 to 0.04, p=0.69). 6 month follow-up (n=285): probability difference: 0.02 (-0.05 to 0.08, p=0.65).

n. Study description: This before/after study among 228 SW living with HIV in the Dominican Republic compared a multi-component intervention, including peer navigators to ensure access to and retention in HIV care services and social support, to standard of care.

o. Indirectness: Downgraded because intervention was multi-component and included individual counseling and health education by psychologists or social workers, sensitivity training for HIV clinical providers, and community mobilization activities at a SW drop-in center, in addition to peer navigation.

p. Risk of bias: Not downgraded for detection bias. Blinding was not possible given the nature of the intervention. Detection bias was unlikely as the outcome was unlikely to have been affected by a lack of blinding.

q. Additional time points: Viral suppression. 3 month follow-up (n=315): probability difference: 0.16 (0.01 to 0.31, p=0.03).

r. Regression coefficient for estimated associations between attendance to peer navigation sessions and achievement of continency management target (HIV undetectable viral load), using a proportional odds ordinal logistic regression. Positive regression coefficient means attending more sessions was associated with greater achievement of target.

References


Hepatitis C testing interval and reinfection incidence

Impact of hepatitis C testing interval on detection of reinfection among key populations: a systematic review and meta-analysis

Authors
Stephanie C Munari*, Michael W Traeger*, Vinay Menon, Ned H Latham, Lakshmi Manoharan, Niklas Luhmann, Rachel Baggaley, Virginia MacDonald, Annette Verster, Nandi Siegfried, Brian Conway, Marina Klein, Julie Bruneau, Mark Stoové, Margaret E Hellard, Joseph S Doyle

* Authors Stephanie C Munari and Michael W Traeger contributed equally to this manuscript

Affiliations:
1 Disease Elimination Program, Burnet Institute, Melbourne, Australia
2 Department of Infectious Diseases, The Alfred Hospital and Monash University, Melbourne, Australia
3 School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia
4 Global HIV, Hepatitis and Sexually Transmitted Infections Programmes, World Health Organization, Geneva, Switzerland
5 Vancouver Infectious Diseases Centre, Vancouver, Canada
6 Department of Medicine, Faculty of Medicine and Health Sciences, McGill University, Montreal, Canada
7 Department of Family Medicine, University of Montreal, Montreal, Canada

Corresponding author:
Stephanie C Munari
85 Commercial Rd, Melbourne, Australia 3004
Email: stephanie.munari@burnet.edu.au
Phone: +61 400 617 570

Alternate corresponding author:
Michael W Traeger
85 Commercial Rd, Melbourne, Australia 3004
Email: michael.traeger@burnet.edu.au
Phone: +61 424 329 324

KEY POINTS: This systematic review evaluates the impact of retesting frequency on the detection of hepatitis C virus reinfection among key populations. Reinfection incidence was highest in studies of MSM and studies reporting a testing interval of every six months or shorter.
Abstract

**Background.** Detecting hepatitis C virus (HCV) reinfection among key populations helps prevent ongoing transmission. Current HCV testing guidelines do not specify recommended testing frequencies in key populations at risk of reinfection. This systematic review aims to estimate the impact of different testing intervals on detection of HCV reinfection.

**Methods.** We searched electronic databases between January 2014 and April 2021 for studies that tested individuals at risk for HCV reinfection at discrete testing intervals and reported HCV reinfection incidence among key populations. Pooled estimates of reinfection incidence rates were calculated by population and testing frequency using random-effects meta-analysis.

**Results.** Thirty-three single-armed observational studies (10,857 individuals) were included. Thirty studies (10,643 individuals) reported HCV reinfection incidence rate per 100 person-years (py) and were included in meta-analyses. The overall pooled estimate of HCV reinfection incidence rate was 4.73 per 100py (95% confidence interval [CI]: 3.68–5.78). The pooled incidence estimate among people who inject drugs (PWID) was 3.94 per 100py (95% CI: 2.83–5.05), among men who have sex with men (MSM) 7.11 per 100py (95% CI: 4.16–10.06) and among people in custodial settings 6.00 per 100py (95% CI: 0.00–12.31). The pooled incidence estimate for studies reporting a testing interval of ≤6 months was higher (5.88 per 100py; 95% CI: 4.14–7.61) than for studies reporting testing intervals >6 months (3.08 per 100py; 95% CI: 1.81–4.35).

**Conclusions.** HCV reinfection incidence was highest in studies of MSM and those which tested at 3–6 month intervals. Shorter testing intervals are likely to identify more infections and be beneficial to preventing onward transmission where treatment is available and enabling progress towards global HCV elimination.

**Trial registration** The review protocol was prospectively registered with PROSPERO (crd42021249863).
## GRADE evidence profile

### GRADE evidence profile for effectiveness review studies - Hepatitis C testing frequency and reinfection incidence

**Author(s):** Michael Traeger, Stephanie Munari, Vinay Menon, Ned Latham, Lakshmi Manoharan, Mark Stoove, Margaret Hellard, Joseph Doyle

**Question:** HCV RNA/cAg tests performed every 3-6 months compared to less frequent testing for diagnosing hepatitis C reinfection in high-risk populations

**Setting:** Key populations including people who inject drugs, men who have sex with men and people in custodial settings

**Bibliography:** See attached list of included studies

<table>
<thead>
<tr>
<th>Nº of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Impact</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall - all studies included in meta-analysis</strong></td>
<td>observational studies</td>
<td>not serious</td>
<td>very serious</td>
<td>serious</td>
<td>not serious</td>
<td>none</td>
<td>4.73 (3.68 - 5.78) IR / 100 person years (95% CI)</td>
<td>⬜️⬜️⬜️⬜️</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>PWID - Overall</strong></td>
<td>observational studies</td>
<td>not serious</td>
<td>very serious</td>
<td>serious</td>
<td>not serious</td>
<td>none</td>
<td>3.94 (2.83 - 5.05) IR / 100 person years (95% CI)</td>
<td>⬜️⬜️⬜️⬜️</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>PWID - 6 months and more frequently (every 3-6 months)</strong></td>
<td>observational studies</td>
<td>not serious</td>
<td>very serious</td>
<td>serious</td>
<td>not serious</td>
<td>none</td>
<td>5.39 (3.47 - 7.31) IR / 100 person years (95% CI)</td>
<td>⬜️⬜️⬜️⬜️</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>PWID - less frequently than 6 months (every 12 months)</strong></td>
<td>observational studies</td>
<td>serious</td>
<td>very serious</td>
<td>serious</td>
<td>not serious</td>
<td>none</td>
<td>1.84 (0.64 - 3.05) IR / 100 person years (95% CI)</td>
<td>⬜️⬜️⬜️⬜️</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>MSM - Overall</strong></td>
<td>observational studies</td>
<td>not serious</td>
<td>serious</td>
<td>serious</td>
<td>serious</td>
<td>none</td>
<td>7.11 (4.16 - 10.06) IR / 100 person years (95% CI)</td>
<td>⬜️⬜️⬜️⬜️</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

38 Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations. Web Annex C. Systematic review findings and GRADE tables
### Certainty assessment

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Impact</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MSM - 6 months and more frequently (every 3-6 months)</strong></td>
<td>3 observational studies</td>
<td>not serious</td>
<td>very serious</td>
<td>serious</td>
<td>serious</td>
<td>none</td>
<td>6.42 (2.33 · 10.50) IR / 100 person years (95% CI)</td>
<td>⊘〇〇〇</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>MSM - less frequently than 6 months (every 12 months)</strong></td>
<td>3 observational studies</td>
<td>serious</td>
<td>serious</td>
<td>serious</td>
<td>serious</td>
<td>none</td>
<td>8.49 (3.24 · 13.74) IR / 100 person years (95% CI)</td>
<td>⊘〇〇〇</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>People in custodial settings - Overall</strong></td>
<td>2 observational studies</td>
<td>not serious</td>
<td>very serious</td>
<td>serious</td>
<td>serious</td>
<td>none</td>
<td>6.00 (0.00 · 12.31) IR / 100 person years (95% CI)</td>
<td>⊘〇〇〇</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

**CI:** Confidence interval

**Explanations**

a. For a full list of included studies please see the attached reference list. All 31 studies are one-armed cohort studies. Populations: PWID (24*), MSM (6*), people in custodial settings (3) * 1 study reports on both PWID and MSM, each arm was included separately in the meta-analysis. Testing interval: every 3m/3-6m/6m (20), every 6-12m/12m (12). Settings: high income country (29), upper middle/high income country (multi-country) (1), upper middle income country (2), low income country (0). Publication year: 2016 (1), 2017 (4), 2018 (6), 2019 (9), 2020 (10), 2021 (2).

b. A modified Newcastle-Ottawa quality assessment scale for cohort studies was used to assess the risk of bias for included studies. Studies were awarded a maximum score of 4 for selection and 5 for outcome, for an overall maximum score of 9.

c. Downgraded by two levels for very serious inconsistency due to large heterogeneity among pooled studies: I-squared = 93.0%, p < 0.001

d. Downgraded by one level for serious indirectness as most studies included PWID and all studies were from high or upper middle income countries.

e. Imprecision was not a major concern, given the large number of participants in the included pooled studies.

f. Downgraded by two levels for very serious inconsistency due to large heterogeneity among pooled studies: I-squared = 92.0%, p < 0.001

g. Downgraded by one level for serious indirectness as all studies were from high or upper middle income countries.

h. Downgraded by two levels for very serious inconsistency due to large heterogeneity among pooled studies: I-squared = 90.6%, p < 0.001

i. Downgraded by one level for serious risk of bias. Kattakuzy, 2020, Sylvestre, 2017, Wyles, 2017 and Berenguer, 2019 (PWID cohort) were at risk of both selection and outcome bias.

j. Downgraded by two levels for very serious inconsistency due to large heterogeneity among pooled studies: I-squared = 86.5%, p < 0.001

k. Downgraded by one level for serious inconsistency due to large heterogeneity among pooled studies: I-squared = 74.2%, p = 0.002
l. Imprecision was downgraded by one level due to a wide confidence interval of the pooled estimate
m. Downgraded by two levels for very serious inconsistency due to large heterogeneity among pooled studies: $I^2 = 82.8\%, p = 0.003$

n. Downgraded by one level for serious risk of bias. Berenguer, 2019 (MSM cohort), Hoorenborg, 2020 and Huang, 2019 were at risk of both selection and outcome bias.
o. Downgraded by one level for serious inconsistency due to large heterogeneity among pooled studies: $I^2 = 63.1\%, p = 0.067$
p. Downgraded by two levels for serious inconsistency due to large heterogeneity among pooled studies: $I^2 = 95.7\%, p < 0.001$

References
Immediate treatment for recent hepatitis C infection

Immediate treatment for recent hepatitis C infection in people with high-risk behaviours: A systematic review and meta-analysis

Authors
Lakshmi Manoharan¹, Ned H Latham¹, Stephanie C Munari¹, Michael W Traeger¹, Vinay Menon¹, Niklas Luhmann⁴, Rachel Baggaley⁴, Virginia MacDonald⁴, Annette Verster⁴, Nandi Siegfried⁴, Gail V Matthews⁵, Mark Stoové², Margaret E Hellard¹-³, Joseph S Doyle¹-²

Affiliations:
¹ Disease Elimination Program, Burnet Institute, Melbourne, Australia
² Department of Infectious Diseases, The Alfred Hospital and Monash University, Melbourne, Australia
³ School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia
⁴ World Health Organization, Global HIV, Hepatitis and Sexually Transmitted Infections Programmes, Geneva, Switzerland
⁵ Kirby Institute, University of New South Wales, Sydney, Australia

Corresponding author:
Lakshmi Manoharan
85 Commercial Rd, Melbourne, Australia 3004
Email: lakshmi.manoharan@burnet.edu.au
Phone: +61 405 101 636

Abstract

Background: Direct-acting antivirals (DAAs) are currently almost exclusively approved for the treatment of chronic hepatitis C virus (HCV). This poses a significant barrier to the treatment of recently acquired hepatitis C. This review aims to determine the benefits and harms of immediate treatment following the detection of recently acquired HCV in people at higher risk of infection.

Methods: A systematic review and meta-analysis was conducted of studies reporting on populations with recently acquired HCV at higher risk of infection. Studies were included if they assessed standard duration DAA treatment regimens for recently acquired HCV and reported on benefits and harms of immediate treatment. Outcomes included SVR12, incidence, treatment imitation and adherence, overtreatment, engagement in care and adverse events.

Results: Twelve studies were included: eight cohort studies, three open label trials and one case series study, reporting on 2085 participants with recently acquired HCV infection. No studies with a comparison group were identified. Eight studies assessed DAA treatment in either men who have sex with men (MSM) or MSM with human immunodeficiency virus (HIV), two studies assessed treatment in people who inject drugs (PWID) and two among people living with HIV (PLHIV).

Immediate treatment of HCV was associated with a pooled SVR12 of 95.9% (95% confidence interval [CI]: 92.6 - 99.3%). Three studies reported on hepatitis C incidence, where most participants in each study were treated in the chronic phase of infection. A treatment completion rate of 100% was reported in two studies and only one serious adverse event was described across all studies.

Conclusion: High rates of cure were achieved with treatment of recently acquired hepatitis C in people at higher risk of infection. Serious adverse events were rare, highlighting individual benefit consistent with the treatment of chronic hepatitis C. The impact of immediate treatment on HCV incidence requires further evaluation.

Trial registration: The review protocol was prospectively registered with PROSPERO (CRD42021239375).
### GRADE evidence profile

#### GRADE evidence profile for effectiveness review studies - Treatment without delay for recent hepatitis C infection

**Author(s):** Ned Latham, Lakshmi Manoharan, Michael Traeger, Stephanie Munari, Vinay Menon, Mark Stoove, Margaret Hellard, Joseph Doyle

**Question:** Should HCV treatment be offered immediately to people with ongoing risk behaviours and recent HCV infection?

**Setting:** Key populations in high-, middle- and low-income countries including (but not limited to): people who inject drugs, men who have sex with men and people in custodial settings

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Impact</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence – people who inject drugs – no studies included this outcome for this population</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>critical</td>
</tr>
<tr>
<td>Incidence - men who have sex with men</td>
<td>3</td>
<td>observational studies</td>
<td>very serious⁹</td>
<td>very serious⁹</td>
<td>very serious⁹</td>
<td>very serious⁹</td>
<td>none</td>
<td>Cotte (2021): Between 2015 - 2018, 141 MSM with recently acquired HCV (from a cohort of 19,945 MSM) were treated. HCV incidence for the cohort increased over time: 0.73 (0.59 - 0.89) in 2015, 0.88 (0.73 - 1.08) in 2016, 0.97 (0.79 - 1.19) in 2017 and 1.25 (1.01 - 1.55) in 2018. Garvey (2021): Between 2016 - 2018, 51 MSM with recently acquired HCV (from a cohort of 9278 MSM) were treated. HCV incidence for the cohort decreased from 1.13 (0.81 - 1.43) in 2016 to 0.46 (0.26 - 0.71) in 2018. Braun (2020): Between 2015 - 2019, 30 acute infections were detected in a cohort of 3538 - 4640 MSM. The number of acute infections treated is not reported. HCV incidence decreased from 0.53 (0.34 - 0.83) in 2014 to 0.12 (0.03 - 0.48) 2019. Incidence expressed per 100 PY for all studies.</td>
<td>☯☐☐☐</td>
</tr>
</tbody>
</table>

[¹] The risk of bias was assessed using the Cochrane Risk of Bias Tool.

[²] These results were based on observational studies.

[³] These results were based on RCTs.

[⁴] These results were based on cohort studies.

[⁵] These results were based on case reports.

[⁶] These results were based on case series.

[⁷] These results were based on case reports and case series.

[⁸] These results were based on cohort studies and case reports.

[⁹] These results were based on RCTs and case reports.

[¹⁰] These results were based on RCTs, cohort studies, case reports and case series.
### Treatment adherence (engagement in care)

<table>
<thead>
<tr>
<th>Nº of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Impact</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>observational studies</td>
<td>very serious¹</td>
<td>not serious</td>
<td>very serious¹</td>
<td>serious⁵</td>
<td>none</td>
<td>Naggie et al. reported 81% adherence (22/27) in PLHIV. Matthews et al. reported adherence rates by risk group: 78% (36/46) in PWID, 84% (55/65) in MSM and 81% (48/59) in PLHIV.³</td>
<td>⊗⊗⊗⊗ ⊙ VERY LOW</td>
<td>critical</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Overtreatment - no studies included this outcome

<table>
<thead>
<tr>
<th>Nº of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Impact</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>important</td>
</tr>
</tbody>
</table>

### Adverse events

<table>
<thead>
<tr>
<th>Nº of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Impact</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>observational studies</td>
<td>very serious¹</td>
<td>not serious</td>
<td>very serious¹</td>
<td>serious⁵</td>
<td>none</td>
<td>Chromy et al. (2019) reported an adverse event rate (grade 2 or less) of 34% (13/38). No treatment-related serious adverse events occurred. Naggie et al. (2019) reported an adverse event rate (grade 2 or grade 3) of 33% (9/27). No treatment-related serious adverse events occurred. Palaniswami et al. (2018) reported an adverse event rate of 36% (9/25) - all reports were “minor headache and fatigue”. Matthews at al. (2021) reported a treatment-related adverse event rate of 22% (21/95). Of these, one was deemed serious (rhabdomyolysis).³</td>
<td>⊗⊗⊗⊗ ⊙ VERY LOW</td>
<td>important</td>
</tr>
</tbody>
</table>

### Treatment completion

<table>
<thead>
<tr>
<th>Nº of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Impact</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>observational studies</td>
<td>very serious¹</td>
<td>not serious</td>
<td>very serious¹</td>
<td>serious⁵</td>
<td>none</td>
<td>Two small studies in people living with HIV (Naggie et al.) and MSM with HIV (Palaniswami et al.) both reported a treatment completion rate of 100%.</td>
<td>⊗⊗⊗⊗ ⊙ VERY LOW</td>
<td>critical</td>
</tr>
</tbody>
</table>
### Certainty assessment

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Impact</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SVR12 - people who inject drugs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>observational studies¹</td>
<td>very serious⁴</td>
<td>not serious⁷</td>
<td>very serious¹</td>
<td>serious⁸</td>
<td>none</td>
<td>Matthews (2021) SVR12: 80.4% (95% CI 66.1 - 90.6)</td>
<td>☎∎∎∎∎</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>SVR12 - men who have sex with men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>observational studies</td>
<td>very serious⁴</td>
<td>serious⁸</td>
<td>very serious¹</td>
<td>not serious</td>
<td>none</td>
<td>Pooled SVR12: 96.9% (95% CI, 93.2 - 100.0)</td>
<td>☎∎∎∎∎</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>SVR12 - people living with HIV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>observational studies</td>
<td>very serious⁴</td>
<td>serious⁸</td>
<td>very serious¹</td>
<td>not serious</td>
<td>none</td>
<td>Pooled SVR12: 97.0% (95% CI 90.7 - 100)</td>
<td>☎∎∎∎∎</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

**Explanations**

a. Risk of Bias: Downgraded twice for very high risk of confounding due to simultaneous treatment of chronic HCV cases within cohort. Also inherently high risk of bias due to lack of comparator group. Joanna Briggs Institute ‘Checklist for Case Series’ used to guide risk of bias assessment.

b. Inconsistency: Downgraded twice for wide variance of point estimates for incidence across studies for pre- and post- intervention periods.

c. Indirectness: Downgraded twice as all three studies reporting incidence were large cohort studies of MSM, however relatively few people within these cohorts were the population of interest (people with recently acquired HCV offered immediate DAA treatment). All three cohorts also included a larger number of MSM with chronic HCV treated with DAAs (e.g. Cotte et al. included 141 treated acute infections vs. 590 treated chronic infections). As people with chronic HCV and ongoing risk behaviour can still transmit the virus to others within the cohort, treating chronic HCV is likely to also influence cohort-level incidence. Given the small number of included studies, it is not possible to disaggregate the effect of treating acute infections on cohort incidence.

d. Imprecision: Downgraded twice for wide, overlapping confidence intervals for incidence pre- and post- intervention.

e. Risk of bias: Downgraded twice as no studies included the comparator of interest (deferral of treatment until onset of chronic infection) and adherence was self- reported - possible recall and social-desirability bias.

f. Indirectness: Downgraded twice as no studies included the comparator of interest (deferral of treatment until onset of chronic infection)

g. Imprecision: Downgraded once due to small sample sizes.

h. Naggie et al. assessed adherence by questionnaire. The adherence figure presented above is calculated on the basis that 5/27 participants reported one or more missed doses in the 4 days preceding the end-of-treatment study visit. Matthews et al. measured adherence by questionnaire and pill count, and defined adherence as ≥95% of scheduled doses for ≥95% of the scheduled treatment period.

i. Risk of bias: Downgraded twice due to lack of comparator group of interest. Method of attribution of adverse event as being treatment related (or not) also not clearly specified in all studies.

j. Adverse event rate for Matthews et al. is for all people with recent HCV treated in the standard treatment duration arm - i.e. includes some people not from PWID/MSM/PLHIV risk groups.
Risk of Bias: Downgraded twice due to lack of comparator group. Joanna Briggs Institute ‘Checklist for Case Series’ also used to guide risk of bias assessment.

Though Matthews et al. was a randomised trial, only one arm was included in this review, as the intervention in the other arm did not meet this review’s inclusion criteria (due to truncated DAA course)

Inconsistency: Not assessed as only one study for this outcome

Imprecision: Downgraded once - wide confidence interval

Inconsistency: Downgraded once - I² = 51.8% p=0.053. We were unable to explain this.

Inconsistency: Downgraded once - I² = 64.8% p=0.059. We were unable to explain this.

Risk of bias: Downgraded twice as unclear whether all acute HCV cases were offered and/or eligible for treatment and no comparator group.

Imprecision: Downgraded once as small number of observed events (treatment initiation).
Pooled screening of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*

*Diagnostic accuracy of pooling urine, anorectal and oropharyngeal specimens for the detection of Chlamydia trachomatis and Neisseria gonorrhoeae: a systematic review and meta-analysis*

**Authors**
Lily Aboud¹,², Yangqi Xu¹, Eric P F Chow²,³,⁴, Teodora Wi⁵, Rachel Baggaley¹, Maeve B Mello⁵, Christopher K Fairley¹,², Jason J Ong⁶,⁷,⁸

**Affiliations:**
¹ College of Medicine and Dentistry, James Cook University, Townsville, Australia.
² Central Clinical School, Monash University, Melbourne, Australia.
³ Melbourne Sexual Health Centre, Alfred Health, Melbourne, Australia.
⁴ Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Australia.
⁵ Global HIV, Hepatitis and STI Programmes, World Health Organization, Geneva, Switzerland.
⁶ Central Clinical School, Monash University, Melbourne, Australia. Jason.ong@monash.edu.
⁷ Melbourne Sexual Health Centre, Alfred Health, Melbourne, Australia. Jason.ong@monash.edu.
⁸ Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK. Jason.ong@monash.edu.

*Contributed equally.*


**Abstract**

**Background**
Screening for *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) at genital and extragenital sites is needed for most key populations, but molecular diagnostic tests for CT/NG are costly. We aimed to determine the accuracy of pooled samples from multiple anatomic sites from one individual to detect CT/NG using the testing of a single sample from one anatomic site as the reference.

**Methods**
In this systematic review and meta-analysis, we searched five databases for articles published from January 1, 2000, to February 4, 2021. Studies were included if they contained original data describing the diagnostic accuracy of pooled testing compared with single samples, resource use, benefits and harms of pooling, acceptability, and impact on health equity. We present the pooled sensitivities and specificities for CT and NG using a bivariate mixed-effects logistic regression model. The study protocol is registered in PROSPERO, an international database of prospectively registered systematic reviews (CRD42021240793). We used GRADE to evaluate the quality of evidence.

**Results**
Our search yielded 7814 studies, with 17 eligible studies included in our review. Most studies were conducted in high-income countries (82.6%, 14/17) and focused on men who have sex with men (70.6%, 12/17). Fourteen studies provided 15 estimates for the meta-analysis for CT with data from 5891 individuals. The pooled sensitivity for multisite pooling for CT was 93.1% [95% confidence intervals (CI) 90.5-95.0], I²=43.3, and pooled specificity was 99.4% [99.0-99.6], I²=52.9. Thirteen studies provided 14 estimates for the meta-analysis for NG with data from 6565 individuals. The pooled sensitivity for multisite pooling for NG was 94.1% [95%...
CI 90.9-96.3], I²=68.4, and pooled specificity was 99.6% [99.1-99.8], I²=83.6. Studies report significant cost savings (by two thirds to a third).

**Conclusion**

Multisite pooled testing is a promising approach to improve testing coverage for CT/NG in resource-constrained settings with a small compromise in sensitivity but with a potential for significant cost savings.
### GRADE evidence profile

**Question:** Should pooled STI testing be used to diagnose *chlamydia* in people at risk for STIs?

<table>
<thead>
<tr>
<th>Outcome</th>
<th>№ of studies (№ of patients)</th>
<th>Study design</th>
<th>Factors that may decrease certainty of evidence</th>
<th>Effect per 1,000 patients tested</th>
<th>Test accuracy CoE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>True positives</strong> (patients with <em>chlamydia</em>)</td>
<td>14 studies 5891 patients</td>
<td>cross-sectional (cohort type accuracy study)</td>
<td>serious&lt;sup&gt;a,b,c&lt;/sup&gt; not serious not serious not serious none</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>False negatives</strong> (patients incorrectly classified as not having <em>chlamydia</em>)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>True negatives</strong> (patients without <em>chlamydia</em>)</td>
<td>14 studies 5891 patients</td>
<td>cross-sectional (cohort type accuracy study)</td>
<td>serious&lt;sup&gt;a,b,c&lt;/sup&gt; not serious not serious not serious none</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>False positives</strong> (patients incorrectly classified as having <em>chlamydia</em>)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Prevalences

<table>
<thead>
<tr>
<th>Prevalences</th>
<th>0%</th>
<th>10%</th>
<th>20%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>0.93 (95% CI: 0.91 to 0.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>0.99 (95% CI: 0.99 to 1.00)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Sensitivity

**Sensitivity**

- **Specificity**

**Specificity**

#### Explanations

- a. Most studies had patient selection bias<sup>1-13</sup> and was scored “high” for risk of bias using the QUADAS checklist in the patient selection criterion as the nature of the study designs and context infers an automatically high risk of selection bias (i.e. patients were not randomised or recruited consecutively).
- b. There were also some studies that had potential for flow and timing bias. In studies by Badman et al.<sup>1</sup> and Dean et al.,<sup>14</sup> if one or more anatomic specimens per participant provided a ‘detected’ result on individual testing, all three samples from that patient were then pooled and retested. This excluded patients who may have attained false-negative results via individual testing. In one study,<sup>10</sup> only 50 of 199 patients had samples pooled. Patient characteristics of those selected not available. Studies by Bristow et al.<sup>2</sup> and Thielemans et al.<sup>11</sup> also had study designs that could decrease the bacterial load of pooled specimens and thus the diagnostic accuracy of the index test. For Bristow et al.,<sup>2</sup> pooled samples were created using remnant aliquots from un-pooled individual samples. Thielemans et al.<sup>11</sup> had all un-pooled individual samples taken before pooled samples.
- c. One study’s pooled specimens were tested by GeneXpert system, whilst un-pooled individual specimens were tested by Cobas system.<sup>8</sup> Re-testing of Cobas negative samples were not undertaken.
References


Question: Should pooled STI testing be used to diagnose gonorrhoea in people at risk for STIs?

<table>
<thead>
<tr>
<th>Outcome</th>
<th>№ of studies (№ of patients)</th>
<th>Study design</th>
<th>Factors that may decrease certainty of evidence</th>
<th>Effect per 1,000 patients tested</th>
<th>Test accuracy CoE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Risk of bias</td>
<td>Indirectness</td>
<td>Inconsistency</td>
</tr>
<tr>
<td>True positives (patients with gonorrhoea)</td>
<td>13 studies 6565 patients</td>
<td>cross-sectional (cohort type accuracy study)</td>
<td>seriousabc</td>
<td>not serious</td>
<td>seriousd</td>
</tr>
<tr>
<td>False negatives (patients incorrectly classified as not having gonorrhoea)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>True negatives (patients without gonorrhoea)</td>
<td>13 studies 6565 patients</td>
<td>cross-sectional (cohort type accuracy study)</td>
<td>seriousabc</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>False positives (patients incorrectly classified as having gonorrhoea)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Explanations:

a. Most studies had patient selection bias and was scored “high” for risk of bias using the QUADAS checklist in the patient selection criterion as the nature of the study designs and context infers an automatically high risk of selection bias (i.e. patients were not randomised or recruited consecutively).

b. There were also some studies that had potential for flow and timing bias. In one study if one or more anatomic specimens per participant provided a ‘detected’ result on individual testing, all three samples from that patient were then pooled and retested. This excluded patients who may have attained false-negative results via individual testing. In one study, only 50 of 199 patients had samples pooled. Patient characteristics of those selected not available. Studies by Bristow et al. and Thielemans et al. also had study designs that could decrease the bacterial load of pooled specimens and thus the diagnostic accuracy of the index test. For Bristow et al., pooled samples were created using remnant aliquots from un-pooled individual samples. Thielemans et al. had all un-pooled individual samples taken before pooled samples.

c. One study’s pooled specimens were tested by GeneXpert system, whilst un-pooled individual specimens were tested by Cobas system. Re-testing of Cobas negative samples were not undertaken.

d. Four studies noted lower sensitivity for pharyngeal gonorrhoea.
References


