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

## Web Annex D. Evidence to decision making tables

World Health Organization

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

## Web Annex D. Evidence to decision making tables

World Health Organization

Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations. Web Annex D. Evidence to decision making tables

ISBN 978-92-4-005346-5 (electronic version)



**Suggested citation.** Web Annex D. Evidence to decision making tables. In: Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

**Cataloguing-in-Publication (CIP) data.** CIP data are available at http://apps.who.int/iris.



This publication forms part of the WHO guideline entitled *Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations*. It is being made publicly available for transparency purposes and information, in accordance with the *WHO handbook for guideline development*, 2nd edition (2014).

Design and layout by Lushomo.

# Contents

# Web Annex D. Evidence to decision making tables

## Counselling behavioural interventions

Evidence to decision making table

| **Question:** Do counselling behavioural interventions reduce risk behaviours associated with transmission or acquisition of HIV, STI and viral hepatitis for people from key populations? | **Judgement** |
|---|---|
| **1. Is the problem a priority?**<br>• 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).<br>• In high-income settings, PWID are thought to be responsible for over 80% of ongoing hepatitis C 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, SW and MSM contributes to HBV and HCV epidemics as well (Nelson et al., 2011; Scheibe et al., 2020).<br>• WHO advocates for STI interventions including strengthening surveillance and screening to be targeted to groups at higher risk (UNAIDS and WHO, 2012; WHO, 2021). | Yes |
| **2. How substantial are the Benefits?**<br>• Range of populations, but mostly focused on HIV/STIs.<br>• Moderate certainty evidence from **6** RCTs among MSM/TG, PWID, and SW in China, Kazakhstan, Kenya, and the USA showed probably **no impact on HIV incidence**.<br>• Low certainty evidence from **1** RCT among SW who inject drugs in Mexico showed there may be **no impact on HIV/STI incidence**.<br>• Moderate certainty evidence from **6** RCTs among PRIS, MSM/TG, MSM, PWID, and SW in China, Kazakhstan, Kenya, and the USA showed probably **no impact on STI incidence**.<br>• Moderate certainty evidence from **1** RCT among PWID in Kazakhstan showed probable **reduction in HCV incidence**, depending on analytic strategy.<br>• Very low certainty evidence from **7** RCTs among PRIS, MSM, PWID, and SW in China, Kazakhstan, Kenya, and the USA showed we are uncertain about the **impact on unsafe sex** (various measures of condomless sex).<br>• Low certainty evidence from **2** RCTs among PWID in Kazakhstan and USA showed there may be **no impact on needle/syringe sharing**.<br>• No studies measured HBV incidence or mortality. | Small, Trivial, Varies |
| **3. How substantial are the Harms?**<br>• No additional data on harms (see #2 above) | Trivial |
| **4. What is the overall certainty of the evidence?**<br>• Moderate certainty | Moderate |

| **Question:** Do counselling behavioural interventions reduce risk behaviours associated with transmission or acquisition of HIV, STI and viral hepatitis for people from key populations? | **Judgement** |
|---|---|
| **5. What is the balance between Benefits and Harms?**<br>• For GDG discussion | Probably / Does not favour either the intervention or the comparison |
| **6. Do people value counselling behavioural interventions?**<br>• Two studies from the USA with MSM and TGD, both focused on HIV, found that participants generally viewed specific counselling behavioural interventions favourably (Moitra et al., 2019; Stephenson et al., 2019).<br>**Key population networks' research:**<br>Overall Findings (all key populations)<br>• Respondents preferred peer-led education, information, counselling and outreach surrounding condom usage, harm reduction, and treatment adherence<br>• Respondents indicated that behavior change interventions should be consistent and that once-off interventions had limited utility, as people's contexts change<br>• Counselling and education were seen as complementary interventions that supported each other in behavior change – but that these interventions had limits<br>• Respondents indicated a need for more health-seeking behaviors when the clinic was non-judgmental and affirming<br>• Peer-led interventions were discussed at length – both benefits and challenges. Some benefits included knowing the language of the community and the community concerns. Some challenges included updating training and information of peers. MPact respondents pointed to peer educators who had outdated or stigmatizing information (such as not knowing about U=U).<br>• Respondents indicated the need for ongoing peer-based and community-led HIV/STI/HCV education delivered through a variety of mechanisms and formats to account for different levels of access, knowledge and literacy and to combined this with counselling and other psychosocial supports for maximum effectiveness<br>• Respondents across all networks indicated that often education efforts are done at one time, when there should be ongoing education efforts as people enter the community at different times or need a refresher<br>• There is a diversity of needs and values amongst KP networks, so what works for one KP might not be appropriate or work for others. INPUD respondents spoke to the importance of motivational interviewing specifically, where MPact respondents brought up ongoing anti-stigma and education efforts.<br>• Respondents spoke about being excluded from behavioral interventions due to their KP identity<br>Population Specific Findings<br>• INPUD and GATE respondents articulated structural barriers – including lack of formal education and literacy as barriers to standard HIV, STI and HCV prevention education.<br>• Participants from the INPUD network further noted that while access to information and education is critical, so too is adequate access to evidence-based harm reduction approaches, such as needle and syringe programs (NSP) and opioid agonist therapy (OAT), to put education into practice.<br>• INPUD network identified the value of counselling and motivational interviewing techniques and the need for a range of different counselling and other behavioural interventions so that people have access to the specific types of support and services they need at different stages. | Probably no important uncertainty or variability, No important uncertainty or variability |

| **Question:** Do counselling behavioural interventions reduce risk behaviours associated with transmission or acquisition of HIV, STI and viral hepatitis for people from key populations? | **Judgement** |
|---|---|
| • GATE and NSWP network members identified economic insecurity as a major risk factor – even when asked about specific behavior change models. This could indicate that the structural barrier to behavior change is integral to attempting any behavior change intervention.<br>• GATE and MPact respondents discussed difficulty in getting gender and sexuality affirming healthcare. This presents a barrier to clinic-based behavior change interventions.<br>Additional Relevant Findings<br>• Law enforcement and punitive laws and policies were identified as contextual factors that inhibit access to prevention and education services<br>• MPact respondents discussed how COVID-19 caused young gay and bisexual men to go back to their family home, disrupting prevention and education on STIs, HIV and HCV<br>• MPact respondents had generally low levels of knowledge about STIs, especially in relationship to their HIV knowledge<br>• Although stressed by INPUD respondents, across all respondents highlighted harm reduction approaches in HIV, STI and HCV prevention throughout - indicating a need to adjust the focus of behavior change interventions. When abstinence is the focus of the behavior change intervention – whether that abstinence is about drug use, sex or other behaviors – then KP respondents could feel excluded and withdraw from the intervention. | |
| **7. How large are the resource requirements (costs)?**<br>• One cost study among SW in Mexico suggests additional cost per participant was US$782 for a single-session intervention and US$3,890 for an annual session.<br>• Another study among PRIS in the USA suggested costs per participant were $689 for the single-session comparison intervention and ranged from $1,823 to 1,836 for a multi-session intervention.<br>• Resource requirements are likely to vary by setting. | (Some) moderate, Varies, Uncertain |
| **8. What is the certainty of the evidence for the costs?**<br>• No evidence | No included studies |
| **9. Are counselling behavioural interventions cost-effective?**<br>• Data from one cost-effectiveness study among SW in Mexico suggests additional cost per QALY gained was US$183 for a single-session intervention and US$1,075 for an annual session of a multi-component intervention<br>• However, this was based on different effectiveness data from the PICO analysis, and for a multi-component intervention which included a counselling behavioural intervention among several other interventions. | Varies, Uncertain |
| **10. What would the impact be on health equity?**<br>• For GDG discussion | Probably increased, Uncertain |
| **11. Are counselling behavioural interventions acceptable to all stakeholders?**<br>• No evidence from systematic review | Probably yes (especially if done by peers) |
| **12. Are counselling behavioural interventions feasible to implement?**<br>• Counselling behavioural interventions are already used in many places, suggesting it is a feasible intervention in many settings. | Yes |

Summary of Guideline Development Group judgements

| | JUDGEMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **PROBLEM** | No | Probably no | Probably yes | **Yes** | | Varies | Uncertain |
| **DESIRABLE EFFECTS** | **Trivial** | **Small** | Moderate | Large | | **Varies** | Uncertain |
| **UNDESIRABLE EFFECTS** | Large | Moderate | Small | **Trivial** | | Varies | Uncertain |
| **CERTAINTY OF EVIDENCE** | Very low | Low | **Moderate** | High | | | No included studies |
| **VALUES** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | **No important uncertainty or variability** | | | |
| **BALANCE OF EFFECTS** | Favors the comparison | Probably favors the comparison | **Probably / Does not favor either the intervention or the comparison** | Probably favors the intervention | Favors the intervention | Varies | **Uncertain** |
| **RESOURCES REQUIRED** | Large costs | **(Some) moderate costs** | Negligible costs and savings | Moderate savings | Large savings | **Varies** | **Uncertain** |
| **CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES** | Very low | Low | Moderate | High | | | **No included studies** |
| **COST EFFECTIVENESS** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | **Varies / Uncertain** | No included studies |
| **EQUITY** | Reduced | Probably reduced | Probably no impact | **Probably increased** | Increased | Varies | **Uncertain** |
| **ACCEPTABILITY** | No | Probably no | **Probably yes (especially if done by peers)** | Yes | | **Varies** | Uncertain |
| **FEASIBILITY** | No | Probably no | Probably yes | **Yes** | | Varies | Uncertain |

# Chemsex

Evidence to decision making table

| **Question:** Do behavioural interventions increase uptake of services and reduce harms associated with Chemsex for key populations? | **Judgement** |
|---|---|
| **1. Is the problem a priority?**<br>• Global need to improve access to and use of prevention, diagnosis, treatment and care services for HIV/VH/STIs among key populations | Probably yes; Yes |
| **2. How substantial are the Benefits?**<br>• No evidence | No included studies |
| **3. How substantial are the Harms?**<br>• No evidence | No included studies |
| **4. What is the overall certainty of the evidence?**<br>• No evidence | No included studies |
| **5. What is the balance between Benefits and Harms?** | Uncertain |
| **6. Do people value behavioural interventions for chemsex?**<br>**Findings from systematic review:**<br>5 studies, all among MSM in high-income countries (Tomkins et al., 2018; Bedi et al., 2020; Herrijgers et al., 2020; Bourne et al., 2015; Tan et al., 2018)<br>• Preference for chemsex-specific services (merging sexual health and drug use services).<br>• Preference for culturally tailored, non-judgmental services for MSM engaging in chemsex.<br>• Positive reactions to an information leaflet in one study.<br>**Findings from the WHO commissioned research conducted by global key population networks:**<br>Overall Findings (all key populations)<br>• Chemsex is not understood in the same way across respondents and regions. MPact respondents in Africa, for instance, referred to alcohol consistently when responding to this question, even after the particular drugs were highlighted by the interviewer. MPact respondents from MENA similarly did not have familiarity with chemsex, and one insisted that poppers were chemsex.<br>• Respondents noted the need to promote awareness and education surrounding chemsex<br>• Respondents discussed the stigma and discrimination towards those who engage in chemsex and noted the need to address it.<br>• Call for tailored, non-judgmental, peer-led interventions and harm reduction approaches (which avoid focusing purely on abstinence) | Possibly important uncertainty or variability;<br>Probably no important uncertainty or variability;<br>No important uncertainty or variability |

| **Question:** Do behavioural interventions increase uptake of services and reduce harms associated with Chemsex for key populations? | **Judgement** |
|---|---|
| Population Specific Findings<br>• Sex workers - including trans sex workers - discussed how chemsex was required on the part of some clients. Respondents identified cocaine and crystal meth as the primary drugs that clients used.<br>• Overall lack of education for sex workers on potential risks of chemsex<br>• People who use drugs articulated a need for a broader sense of ”sexualized drug use” and building “communities of care”<br>• Participants indicated that trans men are often not included in most chemsex interventions focused on gay and bisexual men<br>• Even amongst gay and bi men, respondents had vastly different definitions of chemsex depending on region. Respondents from Africa included alcohol in their definitions, and some discussed the use of poppers as chemsex<br>• MPact Asia Pacific and MENA respondents indicated that chemsex was more common in tourist areas for gay and bisexual men<br>• Service providers do not necessarily have the same connections with KPs due to concealing KP identity and behaviors. Gay and bisexual men and sex workers may conceal their drug using behaviors with service providers<br>Additional Relevant Findings<br>• COVID pandemic lockdowns have had serious impact on drug use and sexual behaviors, as well as lack of access to healthcare and education. People have had difficulty with public health mitigation factors and made them more vulnerable when seeking drugs and sex.<br>• When asked about chemsex, several respondents discussed the context where gay sex can occur especially during COVID-19. “*The few opportunities that we had to get together just disappeared… Black mail and extortion have increased – it’s always been an issue in this country but it’s just skyrocketed. And the violence also … on gay men.*” Gay man, Kenya<br>• The use of drugs and sex is particularly challenging to provide education and services in regions where these behaviors are criminalized. | |
| **7. How large are the resource requirements (costs)?**<br>• No studies were identified in the cost and cost-effectiveness review.<br>• Full programme costs, cost-effectiveness and affordability will likely vary by type of intervention and setting. | Uncertain |
| **8. What is the certainty of the evidence for the costs?**<br>• No evidence | No included studies |
| **9. Are behavioural interventions for chemsex cost-effective?**<br>• No evidence | No included studies |
| **10. What would the impact be on health equity?**<br>• If behavioral interventions for chemsex are effective and acceptable, they may help reduce overall inequalities in HIV/VH/STI acquisition and outcomes for KP.<br>• Otherwise, no clear equity considerations. | Increases; Probably increased; Uncertain |

| **Question:** Do behavioural interventions increase uptake of services and reduce harms associated with Chemsex for key populations? | **Judgement** |
|---|---|
| **11. Are behavioural interventions for chemsex acceptable to all stakeholders?**<br>• No evidence | Yes; Probably yes; Varies; Uncertain |
| **12. Are behavioural interventions for chemsex feasible to implement?**<br>• Behavioural interventions are well established and feasible to implement for other populations. Feasibility will likely differ across settings and populations but is generally feasible. | Probably yes; Varies |

***References***


Bedi A, Sewell C, Fitzpatrick C. Peer-led education may be an effective harm reduction strategy for men who have sex with men engaging in 'chemsex'. Int J STD AIDS. 2020 Mar;31(4):392-393. doi: 10.1177/0956462419898614. PMID: 32126948.

Bourne A, Reid D, Hickson F, Torres-Rueda S, Steinberg P, Weatherburn P. "Chemsex" and harm reduction need among gay men in South London. Int J Drug Policy. 2015 Dec;26(12):1171-6. doi: 10.1016/j.drugpo.2015.07.013. Epub 2015 Jul 26. PMID: 26298332.

Herrijgers C, Poels K, Vandebosch H, Platteau T, van Lankveld J, Florence E. Harm Reduction Practices and Needs in a Belgian Chemsex Context: Findings from a Qualitative Study. Int J Environ Res Public Health. 2020 Dec 4;17(23):9081. doi: 10.3390/ijerph17239081. PMID: 33291855; PMCID: PMC7730975.

Tan RKJ, Wong CM, Chen MI, Chan YY, Bin Ibrahim MA, Lim OZ, Chio MT, Wong CS, Chan RKW, Chua LJ, Choong BCH. Chemsex among gay, bisexual, and other men who have sex with men in Singapore and the challenges ahead: A qualitative study. Int J Drug Policy. 2018 Nov;61:31-37. doi: 10.1016/j.drugpo.2018.10.002. Epub 2018 Oct 26. PMID: 30388567.

Tomkins A, Vivancos R, Ward C, Kliner M. How can those engaging in chemsex best be supported? An online survey to gain intelligence in Greater Manchester. Int J STD AIDS. 2018 Feb;29(2):128-134. doi: 10.1177/0956462417719643. Epub 2017 Jul 10. PMID: 28691863.

Summary of Guideline Development Group judgements

| | JUDGEMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **PROBLEM** | No | Probably no | **Probably yes** | **Yes** | | Varies | Uncertain |
| **DESIRABLE EFFECTS** | Trivial | Small | Moderate | Large | | Varies | **No included studies** |
| **UNDESIRABLE EFFECTS** | Large | Moderate | Small | Trivial | | Varies | **No included studies** |
| **CERTAINTY OF EVIDENCE** | Very low | Low | Moderate | High | | | **No included studies** |
| **VALUES** | Important uncertainty or variability | **Possibly important uncertainty or variability** | **Probably no important uncertainty or variability** | **No important uncertainty or variability** | | | |
| **BALANCE OF EFFECTS** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **Uncertain** |
| **RESOURCES REQUIRED** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | Varies | **Uncertain** |
| **CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES** | Very low | Low | Moderate | High | | | **No included studies** |
| **COST EFFECTIVENESS** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **EQUITY** | Reduced | Probably reduced | Probably no impact | **Probably increased** | **Increased** | Varies | **Uncertain** |
| **ACCEPTABILITY** | No | Probably no | **Probably yes** | **Yes** | | **Varies** | **Uncertain** |
| **FEASIBILITY** | No | Probably no | **Probably yes** | Yes | | **Varies** | Uncertain |

# Online service delivery

Evidence to decision making table

| **Service delivery:** a) Outreach through online platforms, b) Online case management, and c) Targeted online health information | **Judgement** |
|---|---|
| **1. Is the problem a priority?**<br>• Global need to improve access to and use of prevention, diagnosis, treatment and care services for HIV/VH/STIs among key populations<br>• Increasingly, people meet sexual partners, create networks of contacts, and buy and sell drugs online<br>• In some settings, and especially during the COVID pandemic, people are more difficult to reach through traditional face-to-face methods<br>• KP online may be more discreet and seek access to services that provide more privacy – health systems should provide services based on clients' needs and preferences | Yes |
| **2. How substantial are the Benefits?**<br>Note: studies primarily focused on HIV with some STI and VH; study locations were mostly in USA but also Canada, China, and Thailand; study populations were mostly MSM but also TG and PRIS<br>• Outreach through online platforms<br>  • Moderate certainty evidence from 1 observational study among MSM in the USA showed probably more previously unreached people getting reached<br>  • Moderate certainty evidence from 2 RCTs among MSM in China showed a probable increase in HIV testing<br>  • No difference in use of prevention services (high to low certainty) or syphilis testing (moderate certainty)<br>  • No evidence on treatment initiation<br>• Online case management<br>  • Low certainty evidence from 1 observational study among MSM/TG in the USA showed there may be modest improvement in treatment initiation<br>  • Moderate certainty evidence from 1 observational study among PRIS in the USA found probable improvement in viral load<br>  • No difference in use of prevention services (low certainty), uptake of repeat HIV testing (very low certainty), treatment initiation (low certainty), treatment retention/completion (moderate to low certainty), or viral load (low certainty)<br>  • No evidence on cure or mortality<br>• Targeted online health information<br>  • No difference in use of prevention services (very low certainty) or uptake of testing services (low to very low certainty)<br>  • No evidence on treatment initiation, treatment retention/completion, viral load, cure or mortality | Moderate;<br>Varies;<br>Uncertain |

| **Service delivery:** a) Outreach through online platforms, b) Online case management, and c) Targeted online health information | **Judgement** |
|---|---|
| **3. How substantial are the Harms?**<br>• No additional data on harms (see #2 above) | Small; Trivial; Uncertain<br><br>The group discussed there may be large harms not captured in the available data. |
| **4. What is the overall certainty of the evidence?**<br>Outreach through online platforms<br>• High to low<br>Online case management<br>• Moderate to very low<br>Targeted health information<br>• Low to very low | Low |
| **5. What is the balance between Benefits and Harms?**<br>For GDG discussion | Does not favour either (i.e. equally as good as standard of care); Some uncertainty |
| **6. Do people value online service delivery?**<br>• Outreach through online platforms: 3 studies among MSM in high and low/middle income countries found general high acceptability/satisfaction/interest/willingness for outreach to MSM through online platforms e.g. social media, hookup apps/gay mobile apps, email, text message<br>• Online case management: 7 studies among MSM in USA including youth found 1) interest in sexual health features in smartphone apps for finding LGBT-friendly providers, receiving lab results, scheduling appointment reminders, live chatting with providers, receiving medication reminder alerts, etc and 2) when exploring feedback on specific online case management apps, studies generally found high acceptability (though some preferred Google or existing phone functions). They especially appreciated ease of use (easy to navigate, fast, convenient), tools like reminders/alerts/alarms or adherence trackers, and communication with providers which helped them feel supported. MSM also offered constructive feedback on specific designs and problems. Some were concerned with confidentiality.<br>• Targeted online health information: 3 studies among MSM in high income countries found general support for healthcare organizations providing sexual health information through social media/dating apps. MSM expressed a range of acceptability of such targeting, ranging from no impact to frustration to beneficial influencing careseeking/risk behaviours. Generally, MSM were comfortable interacting with health services online (including through platforms that are not typically for health services, like geosocial networking sites e.g. Facebook or dating apps e.g. Grindr). | Possibly important uncertainty or variability; Probably no important uncertainty or variability |

| **Service delivery:** a) Outreach through online platforms, b) Online case management, and c) Targeted online health information | **Judgement** |
|---|---|
| **Key population networks research findings:**<br>Overall findings<br>• participants across key population networks and regions supported the use of online services in addition to in-person services<br>• potential online services could include: information sharing & service linkage through online dating platforms & social media outreach; online ordering systems combined with postal services for medication and harm reduction supplies; and online health appointment scheduling and consultations<br>• online services and platforms cannot replace in-person health services<br>• challenges & digital inequalities might hinder access and uptake of online services reduced access to technology, high data costs, and differing levels of digital competencies<br>Population specific findings<br>• online services can be particularly impactful amongst harder-to-reach sub-populations i.e. young MSM and migrant sex workers (MPact & NSWP)<br>• concerns due to widespread criminalization of drug use & sex work leaving a 'digital footprint' could be used by prosecutors (INPUD & NSWP) | |
| **7. How large are the resource requirements?**<br>Outreach through online platforms: no evidence from systematic review<br>Online case management: no evidence from systematic review<br>Targeted health information<br>• Generally lower cost than standard health interventions (broader reach but potentially higher specificity with targeting)<br>• One study among MSM in Canada found that syphilis testing campaign ads released over one month over four platforms had the lowest cost-per-click ratio on the "hook-up" platforms Grindr and Squirt, compared to more traditional social media platforms like Facebook and the Gay Ad Network.<br>Indirect evidence from FHI360 "Going online budgeting guide" shows a wide range of costs for programs, depending on scope of work, country/regional costs, connectivity level, program intensity/scale, vendors, in-person trips/training needs, equipment needs, etc. | Varies |
| **8. What is the certainty of the evidence for the costs?**<br>• No evidence | No included studies |
| **9. Is online service delivery cost-effective?**<br>• No evidence | No included studies |
| **10. What would the impact be on health equity?**<br>• Outreach, targeting, and service delivery through social media platforms and internet sites will reach individuals who have access to such technology.<br>• Many people globally have access to smartphones and internet, but not all. Those who do not are likely to be particularly poor/marginalized.<br>• Using online interventions may increase access to those who are geographically or otherwise isolated and therefore increase equity | Varies |

| **Service delivery:** a) Outreach through online platforms, b) Online case management, and c) Targeted online health information | **Judgement** |
|---|---|
| **11. Is online service delivery acceptable to all stakeholders?**<br>1 study among service providers for MSM in Canada found:<br>• Online technologies have reshaped the "gay/queer community", changed norms for social/sexual interactions, and can help reach out to hard-to-reach MSM<br>• Online outreach is more non-intrusive and anonymous, yet also responsive to user needs<br>• Online outreach also has some barriers, like quality of service, collaborations between outreach service agencies and companies that own apps and websites, budgetary and staff/volunteer capacity constraints, and data security/safety<br>• Ethical dilemmas: 1) managing personal/professional boundaries with clients, 2) disclosing personal/identifiable information to clients, 3) maintaining client confidentiality and anonymity, 4) security and data storage measures of online information | Probably yes; Varies |
| **12. Is online service delivery feasible to implement?**<br>• Access to the internet and social media apps has grown exponentially in recent years, even in low-income settings.<br>• Multiple studies have used online outreach and targeted messaging to recruit participants into studies, even if they have not been designed to evaluate this outreach approach.<br>• Multiple projects are already using online services for KP, suggesting it is a feasible intervention in many settings. | Yes; Probably yes; Varies |

Summary of Guideline Development Group judgements

| | JUDGEMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **PROBLEM** | No | Probably no | Probably yes | **Yes** | | Varies | Uncertain |
| **DESIRABLE EFFECTS** | Trivial | Small | **Moderate** | Large | | **Varies** | **Uncertain** |
| **UNDESIRABLE EFFECTS** | **Large (potentially not captured in review)** | Moderate | **Small** | **Trivial** | | Varies | **Uncertain** |
| **CERTAINTY OF EVIDENCE** | Very low | **Low** | Moderate | High | | | No included studies |
| **VALUES** | Important uncertainty or variability | **Possibly important uncertainty or variability** | **Probably no important uncertainty or variability** | No important uncertainty or variability | | | |
| **BALANCE OF EFFECTS** | Favors the comparison | Probably favors the comparison | **Does not favor either the intervention or the comparison** | Probably favors the intervention | Favors the intervention | Varies | **(Some) Uncertain** |
| **RESOURCES REQUIRED** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | **Varies** | Uncertain |
| **CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES** | Very low | Low | Moderate | High | | | **No included studies** |
| **COST EFFECTIVENESS** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **EQUITY** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | **Varies** | Uncertain |
| **ACCEPTABILITY** | No | Probably no | **Probably yes** | Yes | | **Varies** | Uncertain |
| **FEASIBILITY** | No | Probably no | **Probably yes** | **Yes** | | **Varies** | Uncertain |

# Peer navigation

Evidence to decision making table

| Question | Judgement |
|---|---|
| **1. Is the problem a priority?**<br>• Key populations are disproportionately affected by HIV, other STIs, and Viral Hepatitis, and often have difficulty accessing treatment<br>• **HIV**<br>  • Globally in 2020, 73% (27.4 million) of people living with HIV were accessing treatment and 66% (24.8 million) were virally suppressed (UNAIDS 2021)<br>  • "Reaching key populations living with HIV with treatment services has been a challenge across regions" (UNAIDS 2021)<br>• **HCV:**<br>  • Only 9.4 million of an estimated 58 million people with chronic HCV have been treated (WHO 2021)<br>  • KP are highly and disproportionally affected<br>  • Strong drop-off after initial diagnosis in care cascade across populations/contexts<br>• **HBV:**<br>  • Only 6.6 million of an estimated 296 million people with chronic HBV have been treated (WHO 2021)<br>• **STIs**<br>  • More than 1 million STIs are acquired each day; key populations are among those who may be "left behind" by STI programs (WHO 2019) | Yes |
| **2. How substantial are the Benefits?**<br>• All studies focused on HIV<br>• Time to diagnosis or linkage to care<br>  • high certainty evidence from 1 RCT among PRIS in the USA found no difference in probability of HIV care visits after jail release<br>  • low certainty evidence from 1 RCT among SW in Tanzania found improvements in ever linkage to care<br>  • moderate certainty evidence from 1 observational study among TG in the USA found improvements in having a first HIV care visit<br>• Treatment retention/completion<br>  • moderate certainty evidence from 1 RCT among PRIS in the USA found no difference in current ART use<br>  • low certainty evidence from 1 RCT and 1 observational study among SW in the Dominican Republic and Tanzania showed modest improvements in current ART use<br>• Viral load<br>  • high certainty evidence from 1 RCT among PRIS in the USA showed improvements in undetectable viral load.<br>  • moderate certainty evidence from 1 RCT and 1 observational study among SW in the Dominican Republic, and Tanzania showed no difference in viral load<br>  • moderate certainty evidence from 1 observational study among TG in the USA found improvement in undetectable viral load<br>• No studies measured the outcomes of treatment initiation, cure, or mortality | Small; Varies |

| Question | Judgement |
|---|---|
| **3. How substantial are the Harms?**<br>• No additional data on harms (see #2 above) | Small; Trivial; Varies |
| **4. What is the overall certainty of the evidence?**<br>• High to low certainty | Moderate |
| **5. What is the balance between Benefits and Harms?** | Probably favours the intervention; Varies; Uncertain |
| **6. Do people value peer navigators?**<br>Key population network values and preferences research found:<br>Overall findings<br>• across all four key population networks the concept of peer navigation was greatly valued<br>• "peer navigators" was not universally recognized by all participants<br>• Other terms such as "peer educators," "peer counsellors," and "peer consultants" were used as well<br>• In some settings, PNs were described as one of the only available option for reaching communities<br>• Peer navigators were positively associated with treatment linkage, continuity, and re-engagement<br>• communication, compassion, first-hand experience, among others were named as key traits of PNs<br>Population specific findings<br>• Importance of having peer navigators with a specific age, gender, cultural, and/or linguistic background (GATE, NSWP, INPUD)<br>• Sustainability and support for their work is lacking for most PNs → work is often done without compensation → this potentially keeps community members from becoming PNs (GATE)<br>• Confidentiality issues were raised → confidential information could be spread within the community (i.e. HIV status) (GATE) | Probably no important uncertainty or variability;<br>No important uncertainty or variability |

| Question | Judgement |
|---|---|
| **7. How large are the resource requirements (costs)?**<br>• No studies were identified in the cost and cost-effectiveness review.<br>• One indirect study from Tanzania (not for KP specifically) estimated cost per client between 18-44 USD<br>• Resource requirements needed may include:<br>  • Cost for full-time salaries of peer navigators<br>  • Cost for additional supervisory staff/staff time<br>  • Potential costs to contract with government or other facilities<br>  • Initial and recurring costs, including mobile phones, SIM cards/credit, and transportation<br>• Peer navigators may cost less than other health professionals to perform the same tasks. However, if peer navigation is added on top of existing services, there may be an increase in total programme costs.<br>• Full programme costs, cost-effectiveness and affordability will likely vary across settings. | No included studies |
| **8. What is the certainty of the evidence for the costs?**<br>• No evidence | No included studies |
| **9. Are peer navigators cost-effective?**<br>• No evidence | No included studies |
| **10. What would the impact be on health equity?**<br>• Peer navigation can help support the most vulnerable populations and increase their health care accessibility<br>• Peer navigators may make clients feel more comfortable with services that meet their specific needs and serve as role models, increasing equity<br>• Potential negative equity impact if peer navigators are paid less (valued less) to conduct the same work as providers<br>• Potential positive equity impact through empowerment of peer navigators themselves | Increased; Probably increased |
| **11. Are peer navigators acceptable to all stakeholders?**<br>• Two qualitative studies with CBO and health workers suggested peer navigators for KP were acceptable and valued, though continued challenges remained to be addressed (e.g. fear that clients may become too dependent and not be able to self-manage, social factors like cultural competence and stigma, police interference). | Yes; Probably yes; Varies |
| **12. Are peer navigators feasible to implement?**<br>• Multiple projects are already using peer navigators, suggesting it is a feasible intervention in many settings.<br>• Training peer navigators does not require extensive time or resources.<br>• Ongoing programme management feasibility will vary across settings. | Yes |

Summary of Guideline Development Group judgements

| | JUDGEMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **PROBLEM** | No | Probably no | Probably yes | **Yes** | | Varies | Uncertain |
| **DESIRABLE EFFECTS** | Trivial | **Small** | Moderate | Large | | **Varies** | Uncertain |
| **UNDESIRABLE EFFECTS** | Large | Moderate | **Small** | **Trivial** | | Varies | **Uncertain** |
| **CERTAINTY OF EVIDENCE** | Very low | Low | **Moderate** | High | | | No included studies |
| **VALUES** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | **No important uncertainty or variability** | | | |
| **BALANCE OF EFFECTS** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favours the intervention** | Favors the intervention | **Varies** | **Uncertain** |
| **RESOURCES REQUIRED** | Large costs | **Moderate costs** | Negligible costs and savings | **Moderate savings** | Large savings | **Varies** | **Uncertain** |
| **CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES** | Very low | Low | Moderate | High | | | **No included studies** |
| **COST EFFECTIVENESS** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **EQUITY** | Reduced | Probably reduced | Probably no impact | **Probably increased** | **Increased** | Varies | Uncertain |
| **ACCEPTABILITY** | No | Probably no | **Probably yes** | **Yes** | | **Varies** | Uncertain |
| **FEASIBILITY** | No | Probably no | Probably yes | **Yes** | | Varies | Uncertain |

# Hepatitis C testing frequency and reinfection incidence

| **Question:** Should HCV treatment with pangenotypic DAAs as recommended by WHO be offered immediately to people with ongoing risk behaviours and recent HCV infection (including recent HCV reinfection)? | |
|---|---|
| **POPULATION:** | Individuals with ongoing risk, with documented evidence of a negative RNA/cAg test (Ab positive or previous infection documented) |
| **INTERVENTION:** | HCV RNA/cAg tests performed every 3-6 months |
| **COMPARISON:** | Less frequent testing |
| **MAIN OUTCOMES:** | Primary outcome: Detection rate of HCV re-infection<br>Secondary outcomes: Testing uptake for viraemia/cAg testing, linkage to clinical assessment and/or treatment initiation following re-infection, risk behaviour, adverse events or social harm |
| **SETTING:** | Priority populations including people who inject drugs, men who have sex with men and people in custodial settings |
| **PERSPECTIVE:** | |
| **BACKGROUND:** | Several national & international guidelines recommend serial testing for hepatitis C re-infection in priority groups, but do not state a specific testing frequency; including WHO guidelines in HBV and HCV testing in 2017 and the US Preventive Services Taskforce Recommendation Statement 2020 [1, 2] |
| **CONFLICT OF INTERESTS:** | None |

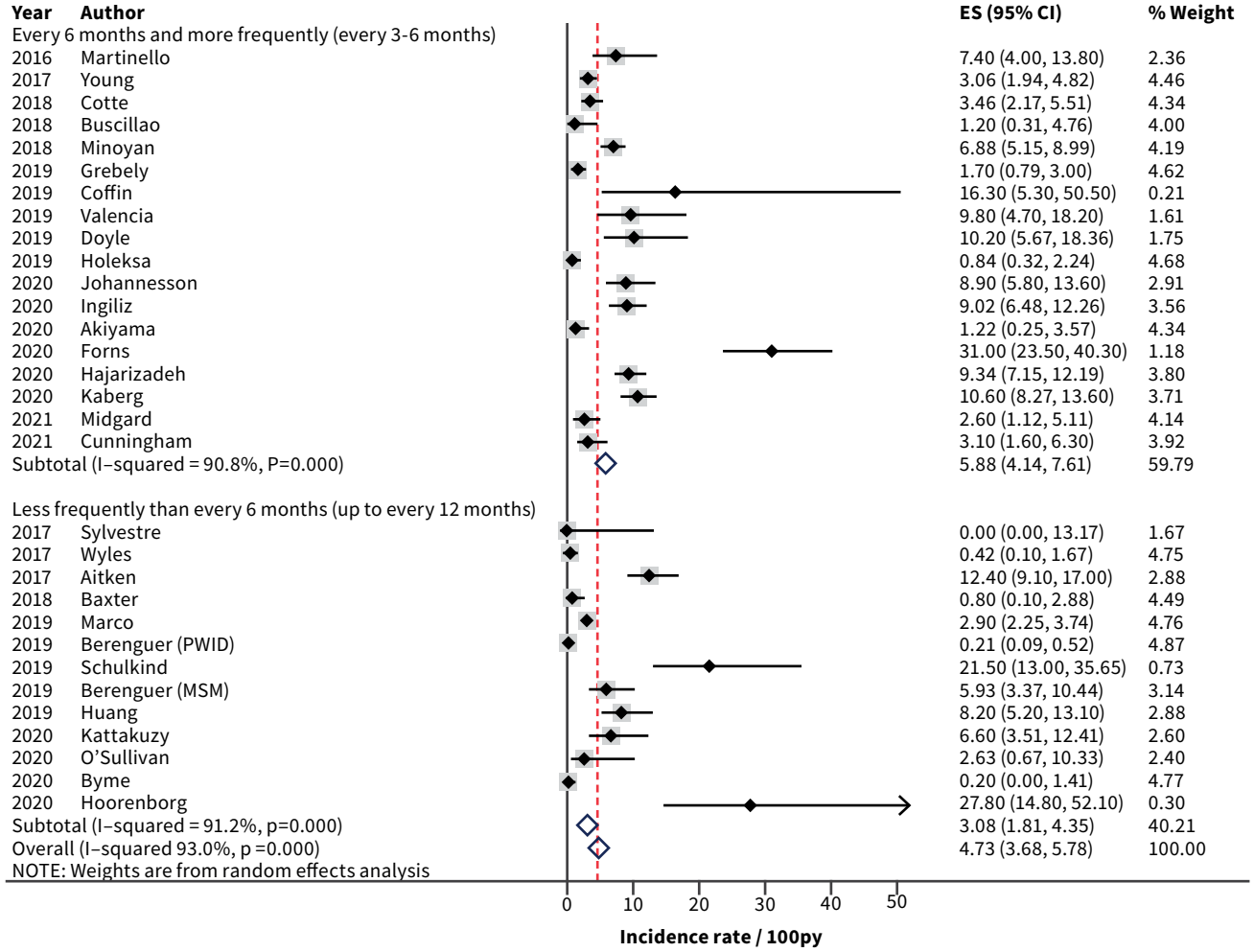
## Assessment

| PROBLEM<br>Is the problem a priority? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Yes | • The WHO has set an HCV elimination target of 80% reduction in HCV incidence by 2030 [3].<br>• Many countries need additional strategies to meet these targets [4].<br>• DAA therapy for HCV infection is highly effective, even in priority groups such as PWID, MSM, and people in custodial settings such as prisons [5].<br>• However, ongoing risk behaviors in groups such as PWID can lead to HCV re-infection, which presents an ongoing challenge to community-wide and global HCV elimination [6].<br>• Several national & international guidelines recommend serial testing for hepatitis C re-infection in priority groups, but do not state a specific testing frequency; including WHO guidelines in HBV and HCV testing in 2017 and the US Preventive Services Taskforce Recommendation Statement 2020 [1,2].<br>• This systematic review aimed to evaluate the current evidence regarding optimum testing frequency for HCV re-infection in priority groups after successful treatment or spontaneous clearance.<br>• Determining this optimum frequency will assist in a treatment as prevention approach to reduce HCV incidence and prevalence. | |

| DESIRABLE EFFECTS<br>How substantial are the desirable anticipated effects? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Moderate / large<br>Some uncertainty | • The objective of this review was to assess the optimal HCV RNA/cAg frequency among individuals with ongoing risk behaviours, with documented evidence of a positive HCV antibody test and a negative HCV RNA/cAg test.<br>• The primary outcome of the study was the re-infection incidence rate.<br>• Our search strategy identified no comparative studies of testing frequencies in this group. However, 32 one-armed studies were identified, which utilised regular testing frequencies to measure the incidence rate of re-infections in these population groups.<br>• We found the most meaningful comparison was between studies testing at 3-6-monthly intervals versus studies testing at greater than 6-monthly intervals.<br>• The following Forest plot provides the re-infection incidence rate for the included studies, and the pooled incidence for *3-6-monthly testing* and *less frequently than 6-monthly* testing: | |

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|

## HCV reinfection incidence, by testing regime



| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | • For studies testing at 3-6-monthly intervals, the mean incidence of re-infection was 5.88 (95% CI 4.14-7.61).<br>• For studies testing at greater than 6-month intervals, the mean incidence of re-infection was 3.08 (95% CI 1.81-4.35).<br>• 3-6 monthly testing was **non-significantly** associated with a higher incidence than less frequently than 6-monthly testing. However, this was most likely because researchers and clinicians were more likely to test patients at higher risk of re-infection.<br>• This finding was of very low certainty. These studies had significant risk of bias due to their observational nature, and very high heterogeneity/inconsistency.<br><br>• Among just PWID, re-infection incidence rates were significantly higher in the group tested 3-6 monthly at 5.39 (3.47-7.31) versus less frequently than 6 months at 1.84 (0.64-3.05). Again, this was likely due to the confounding effects of more high-risk patients being tested more frequently.<br>• Among MSM, there were fewer studies, and re-infection incidence rates were similar between the group tested 3-6-monthly at 6.42 (2.33-10.50) and the group tested less frequently than 6 months at 8.49 (3.24-13.74).<br>• There was insufficient data to make this comparison for other population groups, such as people in custodial settings.<br><br>• Our review also identified 2 modelling studies which were supportive.<br>• Chaillon et al 2019 modelled expanded treatment & post-treatment re-testing of all PWID diagnosed with HCV in India [7]. In sensitivity analyses, they found that more frequent post-treatment testing (ongoing annual testing) was more effective than a one-time retest at one year post-SVR [7].<br>• Castry et al 2020 undertook a modelling study based on a population of HIV-positive MSM in France [8]. The study found that by 2030, 6-monthly population testing led to an 18.5% reduction in HCV re-infection over the baseline scenario of 12-monthly testing. For 3-6 monthly and 3-monthly testing, this reduction was 21.5% and 23.0% respectively [8].<br>• Both studies suggested there were likely desirable effects from more frequent testing, although they are limited as modelling studies.<br><br>• Thus, more frequent testing may have beneficial effects amongst PWID, but the evidence is of very low certainty.<br>• Potential benefits include population-level benefits (reduced HCV incidence and prevalence over time) and better individual outcomes (from early diagnosis).<br>• Patients could potentially benefit from better engagement in the healthcare system for other interventions, such as risk reduction.<br><br>• In summary, for PWID, 3-6 monthly testing was associated with a higher incidence than less frequently than 6-monthly testing. This was not true for other population groups.<br>• However, this was most likely because researchers and clinicians were more likely to test patients at higher risk of re-infection.<br>• Furthermore, these observational studies had very low certainty in addressing our research question. | |

| UNDESIRABLE EFFECTS<br>How substantial are the undesirable anticipated effects? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Small / Trivial<br>Some variation | • Adverse events, social harm, & effects on risk behavior were secondary outcomes of our review. None of our identified studies directly addressed undesirable effects, such as adverse events, social harm, or effects on risk behavior.<br>• The main physical risks of more frequent blood testing for HCV are relatively minor such as short-lived discomfort and bruising.<br>• Stigma, negative psychological impacts and relationship strains have been associated with some healthcare interventions for priority groups such as PWID [9, 10]. More frequent testing may increase or decrease this undesirable effect.<br>• It is unclear if more frequent testing would influence risk behavior.<br>• The very rare risk of false positives should also be considered. | |

| CERTAINTY OF EVIDENCE<br>What is the overall certainty of the evidence of effects? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Very low | • Overall, the evidence that more frequent testing was associated with higher re-infection incidence in PWID was based only on one-armed observational studies, and was of very low certainty.<br>• There were no two-armed studies allowing for direct comparison between more and less frequent testing.<br>• We have assumed that finding higher short-term re-infection incidence would lead to more early treatment, and then lead to greater long-term reduction in community HCV incidence and prevalence. This assumption is also uncertain. | |

| VALUES<br>Is there important uncertainty about or variability in how much people value the main outcomes? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Probably no important uncertainty or variability/<br>No important uncertainty or variability | • Our review did not find specific values and preference information.<br>• Key Population networks research has provided very useful evidence.<br><br>Overall Findings of KP networks:<br>• Preferences regarding HCV RNA re-testing (following a negative result) varied greatly across the three key population networks who included this question in their research. These population networks were the International Network of People Who Use Drugs (INPUD), MPact Global Action for Gay Men's Health and Rights (MPact) and the Global Network of Sex Work Projects (NSWP).<br>• Participants from INPUD, MPact & NSWP highlighted concerns associated with criminalization, stigma, and discrimination, noting that HCV testing/re-testing (regardless of frequency) should always be voluntary: *"You can't impose testing and say to people you must be tested and force people to do things. It must be with information and consent."* Female drug user, Europe<br>*"I think sex workers should be encouraged to be tested when they want, but never forced."* Male sex worker, United Kingdom<br>• Across the 3 networks who asked this question, participants held an overwhelming preference for HCV services (incl. RNA re-testing) to be community-led and available within community settings (incl. peer-based, mobile & outreach), in order to address concerns related to safety, confidentiality, stigma and discrimination, as well as criminalization.<br><br>Population Specific Findings:<br>• MPact participants indicated a lack of protocols and were hesitant to recommend HCV testing frequency without further evidence, information and planning due to concerns about forced testing.<br>• NSWP participants recommended a wide range of preferred HCV testing frequencies – from once a week to once a year – with many participants considering 3-6 months as optimal.<br>• INPUD participants recommended HCV RNA testing every 3 months for the first year following viral clearance, with a variety of participant recommendations thereafter from every 6 months to every 12 months, depending on injecting drug use practices.<br>• Multiple participants from INPUD and one NSWP participant recommended that regular HCV RNA re-testing following cure should be made available and promoted similarly to HIV 'Test and Treat' approaches, with regular monitoring positively promoted, testing facilitated and immediate treatment for those diagnosed encouraged and/or provided on site.<br><br>Additional Relevant Issues:<br>• Several INPUD FGD participants raised concerns about coming forward for HCV RNA re-testing following viral clearance if currently on OAT due to concerns about having to admit to concurrent injecting drug use and/or the risk of punitive responses (e.g. removal from program, etc).<br>• Many INPUD participants (across regions) also emphasized the importance of embedding HCV RNA testing within broader harm reduction approaches to reduce barriers to access.<br>• In line with the above points, participants highlighted the critical importance of community-led PoC HCV RNA testing and DAA treatment services (incl. peer-based, mobile, outreach, postal, etc.) to reduce barriers to access in the mainstream health system: *"Access to tests is needed that is not associated with visiting medical institutions, if a peer-to-peer counsellor and the drug user himself can do this on their own - it is much more convenient and effective."* Female drug user, European region | * Note: GATE did not include this question in their SSI or FGD guides. |

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | • One NSWP participant shared that the [sex worker-led] organisation in which she works runs a mobile clinic offering hepatitis C testing and treatment to sex workers with 92% treatment retention rate among its clients.<br>• Access to HCV RNA testing as well as HCV prevention and DAA treatment in prisons was stressed by several INPUD participants due to high levels of incarceration among people who inject drugs globally. | |
| **BALANCE OF EFFECTS**<br>**Does the balance between desirable and undesirable effects favour the intervention or the comparison?** | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Probably favours the intervention; favours the intervention<br>Some uncertainty | • Our review found very low certainty evidence, from one-armed observational studies and limited modelling studies, in favour of more frequent re-testing in people at ongoing high risk for HCV re-infection, particularly in PWID.<br>• Frequent retesting (and testing) of people at ongoing HCV risk could potentially be an important part of a test and treat strategy with potential population and individual benefits.<br>• We found no studies, within our specific search parameters, suggesting undesirable effects of more frequent HCV re-testing. | |
| **RESOURCES REQUIRED**<br>**How large are the resource requirements (costs)?** | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Moderate costs (upfront)<br>Moderate savings (future)<br>Some uncertainty | • More frequent testing could involve increased short-term costs of tests, cost of outpatient visits including personnel, and if more re-infections are identified, the short-term costs of increased treatment.<br>• Long-term, there may be cost savings by averting costs of advanced hepatitis and liver failure. There is some support from modelling evidence [7,8].<br>Costs are very much dependent on setting.<br>E.g. In many settings RNA and cAg testing remains expensive relative to resources.<br>E.g. in India (lower middle-income country), recent cost estimate for HCV RNA test is USD $108, outpatient visit $20, and 3-month course of generic DAA treatment $900 [7].<br>E.g. in France (high-income country) recent cost estimate for 3-month course of DAA treatment was $34,000 [11].<br>• More frequent testing may also entail opportunity cost for time and attention spent by medical personnel and administrators<br>• More frequent testing for patients post successful DAA Rx may also divert resources away from other testing regimens, such as the larger population of PWID who have not had access to testing or treatment. | |

| CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES<br>What is the certainty of the evidence of resource requirements (costs)? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| No included studies | • There is significant uncertainty in costs due to variation in costs of testing and treatment between settings including low-, middle-, and high-income countries [11,12], changes in DAA and other medication costs over time, and the variable opportunity cost of diverting staff and attention to this testing regime. | |

| COST EFFECTIVENESS<br>Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Probably favors the intervention<br>Favors the intervention<br>Some uncertainty | • In our review, we found no cost-effectiveness evidence from experimental or observational studies in human subjects.<br>• Our search strategy only included studies that addressed our primary outcome of re-infection incidence. Within this study set, we assessed for secondary outcomes such as cost-effectiveness.<br>• Our search strategy identified 1 modelling study that suggested that more frequent annual testing for re-infection of PWID post-treatment was overall cost-saving, compared to a one-time only re-test [7]. | |

| EQUITY<br>What would be the impact on health equity? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Probably increased<br>Increased<br>Some uncertainty | • No studies in our review provided outcome data on health equity.<br>• More frequent testing could potentially increase early diagnosis & treatment of HCV re-infection in priority groups, thus reducing HCV infection for the individual and the community through a treatment-as-prevention approach.<br>• Reduced HCV amongst these priority groups may potentially improve health equity.<br>• Increased testing could potentially increase the burden of medical intervention for patients who may have multiple co-morbidities and a high treatment & investigation burden. Testing should be voluntary, and streamlining medical visits and investigations should always be considered. | |

| ACCEPTABILITY<br>Is the intervention acceptable to key stakeholders? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Probably yes<br>Probably no<br>Uncertain | • Acceptability of more frequent testing was a secondary outcome of our review. We found that none of our identified studies directly addressed acceptability.<br>• Increased testing frequency of testing, especially in the 3-6 monthly range, may be a significant time and resource burden (such as transport costs), which may influence acceptability.<br>• Stigma, negative psychological impacts and relationship strains have been associated with some healthcare interventions for priority groups such as PWID [9, 10]. This may influence acceptability of more frequent testing.<br>• Key population research provided above provides further insights into acceptability (see values and preferences section). | |

| FEASIBILITY<br>Is the intervention feasible to implement? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Probably yes<br>Yes<br>Varies | • Feasibility of more frequent testing was a secondary outcome of our review. None of our identified studies directly addressed feasibility.<br>• RNA and cAg testing accessibility and cost varies widely across settings; thus feasibility is dependent on the context an health system capacities.<br>• In settings (such as community health centres with existing point of care solutions or well-developed linkage services, frequent retesting may be a feasible addition.<br>• Extensive literature documents the difficulty of engaging priority groups such as PWID in healthcare, due to issues such as stigma, distrust of healthcare services, and negative psychological impacts of interventions [9, 10, 12, 13].<br>• More frequent testing could exacerbate this, which could call the feasibility of these testing regimes into question.<br>• Key population research provided above provides further insights into acceptability (see values and preferences section). | |

Summary of Guideline Development Group judgements

| | JUDGEMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **PROBLEM** | No | Probably no | Probably yes | **Yes** | | Varies | Uncertain |
| **DESIRABLE EFFECTS** | Trivial | Small | **Moderate** | **Large** | | Varies | **(Some) Uncertain** |
| **UNDESIRABLE EFFECTS** | Large | Moderate | **Small** | **Trivial** | | Varies | **(Some) Uncertain** |
| **CERTAINTY OF EVIDENCE** | **Very low** | Low | Moderate | High | | | No included studies |
| **VALUES** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | **No important uncertainty or variability** | | | |
| **BALANCE OF EFFECTS** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | **Favors the intervention** | Varies | **Uncertain** |
| **RESOURCES REQUIRED** | Large costs | **Moderate costs** | Negligible costs and savings | **Moderate savings** | Large savings | Varies | **Uncertain** |
| **CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES** | Very low | Low | Moderate | High | | | **No included studies** |
| **COST EFFECTIVENESS** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | **Favors the intervention** | **Varies** | No included studies |
| **EQUITY** | Reduced | Probably reduced | Probably no impact | **Probably increased** | **Increased** | Varies | **Uncertain** |
| **ACCEPTABILITY** | No | Probably no | Probably yes | Yes | | **Varies** | **Uncertain** |
| **FEASIBILITY** | No | Probably no | **Probably yes** | **Yes** | | **Varies** | Uncertain |

***References for evidence to decision table***


World Health Organization, *WHO guidelines on hepatitis B and C testing. Geneva: World Health Organization*. 2017, WHO: Geneva.

US Preventive Services Taskforce, *Final Recommendation Statement Hepatitis C Virus Infection in Adolescents and Adults: Screening*. 2020, USPSTF: Rockville.

Pedrana, A., et al., *The phases of hepatitis C elimination: achieving WHO elimination targets.* The Lancet Gastroenterology & Hepatology, 2021. 6(1): p. 6-8.

Razavi, H., et al., *Global timing of hepatitis C virus elimination in high-income countries.* Liver International, 2019. 40(3).

Expert, N.H.C.T.P. and Reference Committee, *ASHM National Hepatitis C Testing Policy 2020 v1.3.* 2020, Australasian Society for HIV, Viral Hepatitis, and Sexual Health Medicine: Sydney.

Asher, A., et al., *Clinicians' views of hepatitis C virus treatment candidacy with direct-acting antiviral regimens for people who inject drugs.* Substance Use & Misuse, 2016. 51(9): p. 1218-1223.

Chaillon, A., et al., *Cost-effectiveness and budgetary impact of HCV treatment with direct-acting antivirals in India including the risk of reinfection.* PLOS ONE, 2019. 6(14): p. 6.

Castry, M., et al., *Impact of test-and-treat and risk reduction strategies on HCV transmission among MSM living with HIV in France: a modelling approach.* British Medical Journal: Gut, 2020. 0: p. 1-9.

MJ, T., et al., *Benefits and adverse effects of hepatitis C screening: early results of a screening program.* Journal of Public Health Management Practice, 2007. 13(3): p. 263.

Bennett, T., *Treating People Who Inject Drugs: How to Reach a Difficult-to-Engage Population,* in *Hepatology*. 2018, Haelio.

WHO accelerating access to hepatitis C diagnostics and treatment. 2021 04.08.21: Available from: ACCELERATING ACCESS TO HEPATITIS C DIAGNOSTICS AND TREATMENT (WHO.INT)

Barber M., et al. *Price of a hepatitis cure: Cost of production and current prices for direct-acting antivirals in 50 countries.* Journal of Virus Eradication, 2020. 6 (3)

NIHR Applied Research Collaboration West. *The challenges of researching the experiences of people who inject drugs during a pandemic.* 2020 02.08.21]; Available from: HTTPS://ARC-W.NIHR.AC.UK/NEWS/THE-CHALLENGES-OF-RESEARCHING-THE-EXPERIENCES-OF-PEOPLE-WHO-INJECT-DRUGS-DURING-A-PANDEMIC/

Samo, R.N., et al., *Risk Factors for Loss to Follow-Up among People Who Inject Drugs in a Risk Reduction Program at Karachi, Pakistan. A Case-Cohort Study.* PLOS ONE, 2016. Feb 2016

# Treatment without delay for recent hepatitis C infection

Evidence to decision making table

| **Question:** Should HCV treatment be offered immediately to people with ongoing risk behaviours and recent HCV infection? | |
|---|---|
| **POPULATION:** | People at ongoing risk of hepatitis C with recently acquired hepatitis C infection (i.e. infection acquired within the prior 12 months) |
| **INTERVENTION:** | Immediate treatment with any approved duration of direct-acting antiviral medication |
| **COMPARISON:** | Delayed treatment (or no comparator) |
| **MAIN OUTCOMES:** | Hepatitis C incidence, treatment initiation, engagement in care (adherence), overtreatment, adverse events, treatment completion, SVR12 |
| **SETTING:** | Key populations in high-, middle- and low- income countries including (but not limited to):<br>• people who inject drugs<br>• men who have sex with men<br>• people in custodial settings |
| **BACKGROUND:** | Current WHO treatment guidelines **do not** offer a recommendation as to whether immediate treatment of recent infection should be offered when recently acquired HCV is diagnosed. For people with ongoing risk behaviour, offering immediate treatment reduces opportunities for onward transmission. Deferring treatment until onset of chronic infection allows transmission to others to occur in the interim and introduces additional opportunities for loss to follow-up. |
| **CONFLICTS OF INTEREST:** | Nil |

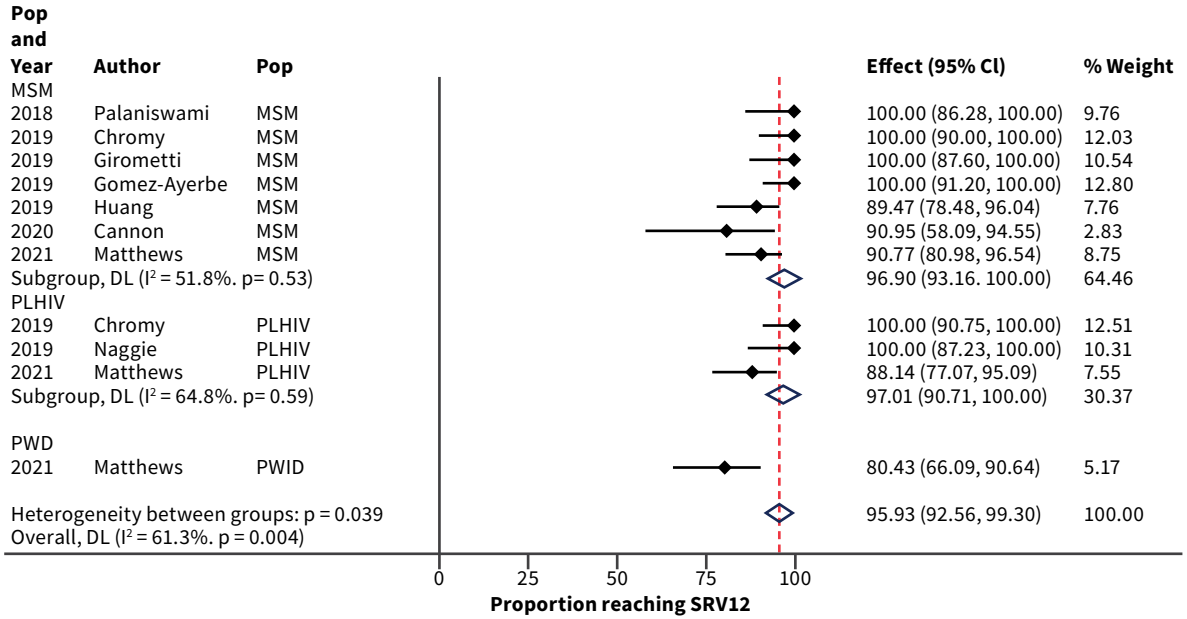
## Assessment

| PROBLEM<br>Is the problem a priority? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Yes | • Worldwide, there are approximately 58 million people living with chronic hepatitis C (1)<br>• Approximately 1.5 million people were newly infected with chronic hepatitis C in 2019 (2)<br>• The World Health Organization Global Health Strategy on Viral Hepatitis 2016-2021, includes a target to reduce hepatitis C incidence by 80% by 2030. (3).<br>• Treating people at ongoing risk of transmitting the virus is critical to achieving elimination goals.(4)<br>• Regular testing and early treatment reduces opportunities for onward transmission.<br>• DAA treatment is not currently approved by most regulators for the treatment of acute/recently-acquired hepatitis C.(5), although clinical guidelines from peak-bodies in Europe and the United States recommend immediate treatment.(6, 7)<br>• For people with ongoing risk behaviour, deferring treatment until onset of chronic infection allows transmission to others to occur in the interim and introduces additional opportunities for loss to follow-up. | |

| DESIRABLE EFFECTS<br>How substantial are the desirable anticipated effects? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Uncertain, but treatment has large benefits;<br>Moderate at individual, large at population level | No studies included in the review compared immediate treatment of recently acquired hepatitis C with deferral of treatment until onset of chronic infection.<br>Desirable effects of immediate treatment include:<br>For the individual<br>• People treated in the included studies achieved high rates of cure (see forest plot below), consistent with the rates of cure seen for direct acting antivirals in chronic hepatitis C in key risk groups. | |

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|

## SVR12



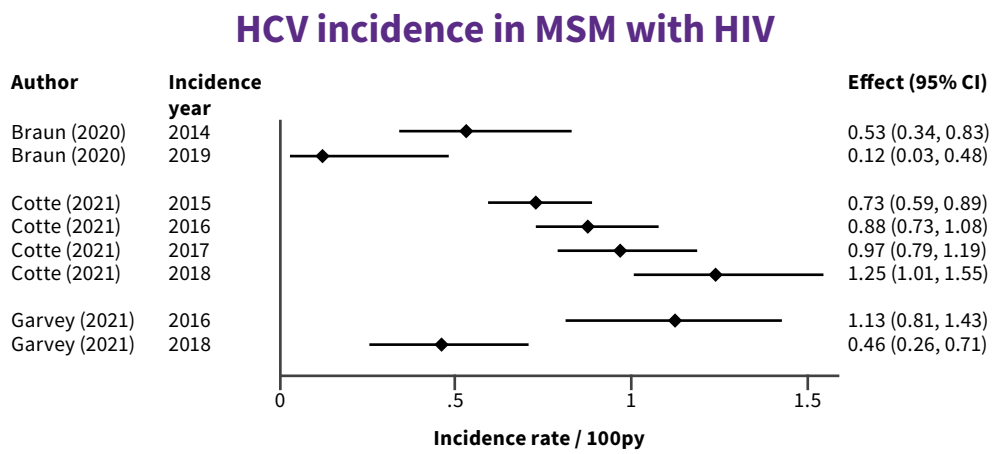

Note: Weights and between-subgroup heterogeneity tests are from random-effects model.

- Treatment adherence was high (81%) in both of the included studies that reported this outcome.
- For individuals newly diagnosed with recently acquired hepatitis C, being treated immediately brings forward the date at which they will be cured. This may have psychological benefits, particularly given the stigma associated with hepatitis C.
- Although no comparative data are available, given the natural history of liver fibrosis/cirrhosis, it is unlikely that immediate treatment compared to delaying treatment by 6-12 months would confer a desirable long-term effect on liver health.
- It is possible that treating people with recently acquired hepatitis C immediately, may also reduce the duration of treatment required to achieve cure by 2 weeks.(5) Experimental/truncated DAA treatment courses were beyond the scope of this review, however if shorter DAA courses for recently acquired HCV are shown to be effective and are approved then the reduced pill-burden may be an additional desirable effect of immediate treatment

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|

### For the population

- Two studies in which people received immediate treatment for acute HCV reported a decline in incidence over time, however one study reported an increase in incidence (see plot below).
- It is critical to note that the three studies reporting incidence were large cohort studies of MSM in which relatively few people were the population of interest (people with recently acquired HCV offered immediate DAA treatment).
- All three cohorts 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.




- A model of immediate treatment of recent HCV in MSM with HIV in the Netherlands, noted a reduction in incidence from 1.2/100 py to 0.2/100 py after 20 years (88% reduction in incidence compared to treatment at F2 stage of liver disease) (8).

| UNDESIRABLE EFFECTS<br>How substantial are the undesirable anticipated effects? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Small or trivial but some over-treatment. | Adverse events<br>• Treatment-related adverse event rates in the four included studies were between 22 - 36%.<br>• Fatigue was the most frequently reported adverse event in three of the four included studies.<br>• All but one of the adverse events were classified as 'non-serious'.<br><br>Overtreatment<br>• No studies reported overtreatment as an outcome<br>• Following infection with hepatitis C, approximately one quarter of individuals will spontaneously clear the virus (i.e. cure without any medical intervention). (9)<br>• Spontaneous clearance largely occurs in the acute (initial 6 months) phase of hepatitis C infection, with a median time to clearance of 16.5 weeks. Spontaneous clearance is more likely to occur in women, genotype 1 infection, and people with clinical evidence of acute hepatitis. (10)<br>• Treating all people with recently acquired hepatitis C immediately, means that people that would have otherwise cleared their infection spontaneously are unnecessarily exposed to the risk of adverse events. This undesirable effect is greatest for the aforementioned groups for that are more likely to clear the infection spontaneously. Conversely, this undesirable effect will occur less frequently in people with HIV, who are less likely to achieve spontaneous clearance.(11) | |

| CERTAINTY OF EVIDENCE<br>What is the overall certainty of the evidence of effects? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Very low | • Data were available from 12 one armed observational studies. No comparator groups were included in the study design.<br>• No studies compared immediate treatment of recently acquired hepatitis C with deferring treatment until the onset of chronic infection.<br>• Overall, there was a very low certainty of evidence for review outcomes.<br>• The three studies which reported on incidence were set in large cohorts of MSM where treated acute infections made up a minority of treated patients (most patients were treated in the chronic phase of infection). Two of these studies showed a decrease in incidence, one showed an increase in incidence. Inferences should not be drawn about changes in incidence as a result of patients treated in the acute phase.<br>• The majority of studies were set in the MSM risk group.<br>• All studies are from high income countries<br>• Two studies reported on PWID.<br>• No studies were set in custodial settings; no studies identified for sex workers or transgender people. | WHO currently strongly recommends offering treatment to all individuals diagnosed with HCV infection who are 12 years of age or older, irrespective of disease stage based on moderate certainty of evidence.<br><br>Age groups being updated in 2022. |

| VALUES<br>Is there important uncertainty about or variability in how much people value the intervention? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| No/probably important uncertainty (key populations want to access and be treated); no known undesirable outcomes. | Values and preferences were not reported in any of the included papers.<br>**Evidence was generated from research by key population networks:**<br>Overall Findings (all key populations)<br>• Awareness and access to pan-genotypic DAAs for HCV treatment **varied significantly** across key populations and regions.<br>• Reported **ongoing barriers to DAA treatment** access and utilization of HCV services:<br>  • cost of HCV treatment<br>  • delays in access to treatment medications<br>  • stigma and discrimination<br>  • lack of research and political will<br>• There was **strong support for immediate access to pan-genotypic DAA treatment** together with education & research to guide implementation and raise awareness.<br>• Some participants identified the importance of immediate DAA treatment **upon confirmation of HCV viremia**:<br>  • No participants raised concerns about potential for over-treatment and were more concerned about lack of access to DAA treatment<br>Population Specific Findings<br>• INPUD participants were the **most knowledgeable and supportive** of pan-genotypic DAA treatment for HCV.<br>• Most INPUD SSI & FGD participants supported offering pan-genotypic DAA treatment immediately to those with recent HCV infection, **regardless of previous viral clearance**.<br>• Some participants stated pan-genotypic DAA treatment **should not be delayed** (even for a short time) to wait for the possibility of viral clearance without treatment due to concerns re: loss to follow-up & potential for ongoing transmission.<br>• INPUD participants from LMIC stressed that **delays to medications can act as barrier to treatment** (quote)<br>*"We have treatment for HCV but it can take up to 3 months to get on the medication because they run a lot of tests and treat the other illnesses you might have first before you get the HCV medication. Therefore, many of my friends are discouraged from getting the treatment altogether."* Female drug user, Africa.<br>Additional Relevant Findings<br>• Significant **ongoing barriers to HCV DAA treatment** remain, particularly in LMIC.<br>• INPUD participants strongly supported **innovative service models** to expand immediate HCV pan-genotypic DAA treatment access: *Eg: peer-based and Rapid Point of Care (PoC) HCV RNA testing to support immediate/same day HCV diagnosis and treatment initiation.*<br>• Potential for 're-infection' and/or requirements to cease drug use and/or OAT **should not be treatment criterion** (quotes). | * Note: GATE did not include this question in their SSI or FGD guides. |

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | • INPUD participants stressed the importance of **harm reduction-based HCV prevention**.<br>• Some NSWP, MPact & GATE participants **had not even heard of HCV pan-genotypic DAA treatment**s. GATE noted most trans people are unaware of hepatitis C.<br><br>*"They also want you to stop using for you to get treatment. They also say things like if you get re-infected, they will not treat you again."* Female drug user, Africa.<br>*"I actually had to sign something that was so intrusive. If I was going to receive treatment, I could not be tested positive for any type of drug in my system..."* Female sex worker, Americas | |
| **BALANCE OF EFFECTS**<br>**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Favours intervention; some uncertainty. | None of the studies compared immediate to deferred treatment. In considering whether to treat people with ongoing risk behaviours immediately following the diagnosis of recently acquired HCV one needs to primarily balance:<br>• the benefit to the individual of being cured as soon as possible after diagnosis, rather than having to wait to access treatment and the associated risk of loss to follow-up.<br>• the benefit to the broader population from curing the person as soon as possible, namely, reducing the period of time for which they are infectious and, in turn, potentially reducing HCV incidence.<br>• the adverse effects of treatment in individuals that would have gone on to clear the virus spontaneously.<br>• the additional cost to individuals and society of expanding DAA access to people with recently acquired infection<br>Key population research provided above provides further insights into acceptability and undesirable effects (see values and preferences section). | |
| **RESOURCES REQUIRED**<br>**How large are the resource requirements (costs)?** | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Moderate costs upfront; Moderate savings in the long term; Varies (context) | DAA costs:<br>• Prices of DAA treatment regimes vary widely across countries.<br>• Pricing depends on whether generic DAAs are available. Local production of generic DAAs is only possible where DAAs are not under patent protection. E.g. for SOF/VEL, cost of a 12 week course varied between countries: US $156 in Pakistan, US $900 in Rwanda and $US 1470 in Brazil.(12) In France, a course of SOF/VEL cost US $ 27,972.(13) | |

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | Service delivery costs:<br>• Immediate treatment of HCV may increase the frequency and hence cost of testing, outpatient visits, and the costs of medical personnel and training staff<br>• Opportunity economic and human costs of diverting resources to increased HCV testing and treatment.<br>• There may be a potential negative effect on care and treatment of other diseases as resources are diverted.<br>• HCV rapid diagnostic tests (WHO prequalified) ranged between US$1 and $8, laboratory based immunoassays between US$1 and $2. (12)<br>• Fixed costs of an analyser ranged between US $10 000 to $25 000. (12) | |
| **CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES**<br>**What is the certainty of the evidence of resource requirements (costs)?** | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| | There is substantial uncertainty regarding evidence for costs associated with treatment of recently acquired HCV. Costs of DAAs and service provision vary widely depending on setting, and the opportunity economic and human costs would also vary depending on population and setting.(12) | |
| **COST EFFECTIVENESS**<br>**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Favours / probably favours intervention; some varies | • Popping et al., 2019 (modelling study in Dutch context amongst HIV positive MSM) **immediate DAA treatment is cost saving compared to delaying treatment to F2**. Earlier treatment will cost society 68.3 million euro over 40 years, compared to 75.1 and 98.4 million euro for delaying treatment awaiting spontaneous clearance and delaying treatment until F2 stage, respectively. This study model reported immediate treatment will prevent 7070 new infections and gain 3419 QALYs compared to F2 treatment with resulting cost saving ICER. (8)<br>• Liu et al., 2020 (modelling study based on Chinese context amongst PWID) **treating acute HCV is highly cost effective and cost saving compared to deferring treatment to the chronic stage**. The ICER for treating acute infection was lower compared to both treatment at the chronic stage without fibrosis, and those with advanced-stage fibrosis.(14)<br>• Bethea et al., 2018 (modelling study based on US scenario amongst acute HCV patient population) reported **treating acute HCV was cost-effective compared to deferring until the chronic phase in patients at-risk**. However, there were increased costs associated with acute HCV treatment in patients who were not at risk of transmitting HCV.(15)<br>• Cost effectiveness depends on the setting context, price of DAAs as well as HCV testing frequency. | |

| EQUITY<br>What would be the impact on health equity? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Increased / Probably increased | • Providing DAA treatment to people with recently-acquired hepatitis C expands choice (i.e. by providing a second option to deferral of treatment until chronic infection) for people from stigmatised groups including PWID and MSM.<br>• Improved identification and treatment of recent infection could potentially increase early diagnosis & treatment of HCV re-infection in high-risk, vulnerable groups, thus reducing HCV infection for the individual & the community through a treatment-as-prevention approach.<br>• Inherent in routinely treating people with recently acquired hepatitis C immediately is overtreatment - i.e. treating individuals that would gone on to achieve spontaneous clearance. As spontaneous clearance is more common in women, overtreatment and any associated harms are more likely to occur more frequently in women.<br>• In settings where access to DAAs is limited, implementing immediate treatment for people with recently acquired infection without increasing overall DAA supply may have a negative health equity impact in the event that DAAs are re-allocated from people with chronic hepatitis C (who are beyond the point of spontaneous clearance and require treatment to prevent future morbidity and mortality) to people with recently acquired hepatitis, who may not necessarily require treatment (due to the remaining possibility of spontaneous clearance) | |
| **ACCEPTABILITY**<br>**Is the intervention acceptable to key stakeholders?** | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Yes and uncertain (no data) | • Acceptability was not reported in any of the included papers.<br>• It is possible that exposing oneself to the risk of adverse events - however mild - may be unacceptable to people with recently acquired hepatitis C if the possibility of achieving spontaneous clearance has not yet been exhausted.<br>• Providing individuals with choice between immediate and deferred treatment is likely to be acceptable to people living with hepatitis C.<br>• It is unknown whether routinely prescribing a treatment to individuals with recently acquired hepatitis C without a period of observation for spontaneous clearance is acceptable to clinicians. | |

| FEASIBILITY<br>Is the intervention feasible to implement? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Yes | • Feasibility of immediate treatment of HCV was not reported in any of the included papers.<br>• For immediate treatment to be feasible, active testing is required to identify HCV seroconversion as well as repeated testing over time. This may be particularly challenging in low resource settings. Feasibility will depend greatly on context and health systems capacities.<br>• In settings (such as community health centers) with existing services for HCV testing and treatment or well-developed linkage services, early treatment may be more feasible.<br>• The studies identified in this review were set in high income countries. There was a lack of evidence regarding the benefits and harms of immediate treatment in low income settings. | |

***References for evidence to decision table***


1. World Health Organization. Hepatitis C Key Facts. Geneva; 2021.
2. World Health Organization. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. Geneva; 2021.
3. World Health Organization. Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis. 2016.
4. Pitcher, Ashley B, Borquez, Annick, Skaathun, Britt, Martin, Natasha K. Mathematical modeling of hepatitis c virus (HCV) prevention among people who inject drugs: A review of the literature and insights for elimination strategies. Journal of theoretical biology; 2019.
5. Martinello, Marianne, Orkin, Chloe, Cooke, Graham, Bhagani, Sanjay, Gane, Edward, Kulasegaram, Ranjababu, Shaw, David, Tu, Elise, Petoumenos, Kathy, Marks, Philippa, Grebely, Jason, Dore, Gregory J., Nelson, Mark, Matthews, Gail V.. Short-Duration Pan-Genotypic Therapy With Glecaprevir/Pibrentasvir for 6 Weeks Among People With Recent Hepatitis C Viral Infection. Hepatology; 2020.
6. AASLD-IDSA Guidance Panel, . Hepatitis C Guidance 2020 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Clin Infect Dis.; 2020.
7. European Association for the Study of the Liver, . EASL recommendations on treatment of hepatitis C: Final update of the series. J Hepatol; 2020.
8. Popping, Stephanie, Hullegie, Sebastiaan J, Boerekamps, Anne, Rijnders, Bart J A, de Knegt, Robert J, Rockstroh, Jürgen K, Verbon, Annelies, Boucher, Charles A B, Nichols, Brooke E, van de Vijver, David A M C. Early treatment of acute hepatitis C infection is cost-effective in HIV-infected men-who-have-sex-with-men. PloS one; 2019.
9. Micallef JM, Kaldor JM,Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies.. J Viral Hepat.; 2006.
10. Grebely, Jason, Page, Kimberly, Sacks-Davis, Rachel, van der Loeff, Maarten Schim, Rice, Thomas M, Bruneau, Julie, Morris, Meghan D, Hajarizadeh, Behzad, Amin, Janaki, Cox, Andrea L, Kim, Arthur Y, McGovern, Barbara H, Schinkel, Janke, George, Jacob, Shoukry, Naglaa H, Lauer, Georg M, Maher, Lisa, Lloyd, Andrew R, Hellard, Margaret, Dore, Gregory J, Prins, Maria, Group, InC3,Study. The effects of female sex, viral genotype, and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection. Hepatology (Baltimore, Md.); 2014.
11. Grebely, Jason, Raffa, Jesse D, Lai, Calvin, Krajden, Mel, Conway, Brian, Tyndall, Mark W. Factors associated with spontaneous clearance of hepatitis C virus among illicit drug users. Canadian journal of gastroenterology; 2007.
12. World Health Organisation, . Accelerating access to hepatitis C diagnostics and treatment: overcoming barriers in low- and middle-income countries. Global progress report 2020. Geneva; 2021.
13. Barber, Melissa J., Gotham, Dzintars, Khwairakpam, Giten, Hill, Andrew. Price of a hepatitis C cure: Cost of production and current prices for direct-acting antivirals in 50 countries. Journal of Virus Eradication; 2020.
14. Liu, Yin, Zhang, Hui, Zhang, Lei, Zou, Xia, Ling, Li. Economic Evaluation of Hepatitis C Treatment Extension to Acute Infection and Early-Stage Fibrosis Among Patients Who Inject Drugs in Developing Countries: A Case of China. International journal of environmental research and public health; 2020.
15. Bethea, Emily D, Chen, Qiushi, Hur, Chin, Chung, Raymond T, Chhatwal, Jagpreet. Should we treat acute hepatitis C? A decision and cost-effectiveness analysis. Hepatology (Baltimore, Md.); 2018

Summary of Guideline Development Group judgements

| | JUDGEMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **PROBLEM** | No | Probably no | Probably yes | **Yes** | | Varies | Uncertain |
| **DESIRABLE EFFECTS** | Trivial | Small | **Moderate (individual level)** | **Large (treatment benefit / population level)** | | Varies | **Uncertain** |
| **UNDESIRABLE EFFECTS** | Large | Moderate | **Small** | **Trivial** | | Varies | Uncertain |
| **CERTAINTY OF EVIDENCE** | **Very low** | Low | Moderate | High | | | No included studies |
| **VALUES** | Important uncertainty or variability | Possibly important uncertainty or variability | Probably no important uncertainty or variability | No important uncertainty or variability | | | |
| **BALANCE OF EFFECTS** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | **Favors the intervention** | Varies | **(Some) uncertain** |
| **RESOURCES REQUIRED** | Large costs | **Moderate costs (upfront)** | Negligible costs and savings | **Moderate savings (long term)** | Large savings | **Varies** | Uncertain |
| **CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES** | Very low | Low | Moderate | High | | | **No included studies** |
| **COST EFFECTIVENESS** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | **Favors the intervention** | Varies | No included studies |
| **EQUITY** | Reduced | Probably reduced | Probably no impact | **Probably increased** | **Increased** | Varies | Uncertain |
| **ACCEPTABILITY** | No | Probably no | Probably yes | **Yes** | | Varies | **Uncertain** |
| **FEASIBILITY** | No | Probably no | Probably yes | **Yes** | | Varies | Uncertain |

# Pooled screening of Chlamydia trachomatis and Neisseria gonorrhoeae

Evidence to decision making table

| **PICO question:** Should pooling of samples from three anatomic sites (urethra, anal and pharynx) be used for STI laboratory screening of gonorrhoea and chlamydial infection over individual samples from three anatomic sites? | |
|---|---|
| **POPULATION:** | Men who have sex with men (MSM), and sex workers (SW) persons who inject drugs (PWID), transgender persons, and incarcerated persons.<br><br>Populations will be disaggregated by geographical location, background STI prevalence, gender, and age group where possible. |
| **INTERVENTION:** | Pooled samples from combined two or three anatomic sites (urethra, anorectum, pharynx) for laboratory screening of *N. gonorrhoeae* and *C. trachomatis*. |
| **COMPARISON:** | Individual samples from three separate anatomic sites (urethra, anorectum, pharynx) for laboratory screening of *N. gonorrhoeae* and *C. trachomatis* |
| **MAIN OUTCOMES:** | True positives<br>True negatives<br>False positives<br>False negatives |
| **SETTING:** | **NO RESTRICTIONS** |
| **PERSPECTIVE:** | **PATIENT AND PROVIDER** |
| **BACKGROUND:** | • More than 1 million curable sexually transmitted infections (STIs) are acquired every day worldwide, primarily caused by *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Treponema pallidum*, and *Trichomonas vaginalis*. Data from the 2021 WHO Global progress report on HIV, viral hepatitis, and sexually transmitted infections indicate a global incidence of 128 million new chlamydia and 82 million new gonorrhoea cases in 2020.(1)<br>• Representing neglected pandemics, these infections cause a significant global disease burden. Population groups vulnerable to acquiring STIs include men who have sex with men (MSM), sex workers (SW) and their clients, people who inject drugs (PWID), transgender people (TG), and incarcerated people.(2-5)<br>• Major gaps persist in the availability of diagnosis and treatment for common curable STIs, with programmes generally underfunded despite high levels of morbidity and mortality from STIs.<br>• Due to cost of diagnostic test, tests are either not conducted or only single site (usually urethral or vaginal) which misses a significant proportion of extra-genital STIs |
| **CONFLICT OF INTERESTS:** | None |

## Assessment

| PROBLEM<br>Is the problem a priority? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Yes | • To control STIs, earlier detection and treatment is needed.<br>• Syndromic treatment misses asymptomatic cases and also results in overtreatment of non-pathological symptoms e.g. vaginal discharge.<br>• Chlamydia and gonorrhoea can increase the risk for acquiring HIV, as increased viral loads of HIV can be found in genital tracts during STI.(6, 7)<br>• Antimicrobial resistance in STIs is rising.(8) For example, inappropriate management of extragenital NG may accelerate the emergence of multidrug resistant NG.(9) This underscores the need for aetiological diagnosis to optimize STI management.<br>• Aetiological diagnosis that tests all appropriate anatomical sites is needed. Evaluation for CT/NG at extragenital sites is critical for key populations, as a significant proportion of infections would be missed if only genital screening were undertaken.(10) Studies have demonstrated that up to one-third of NG cases would be missed if only urethral or urine samples were tested in MSM.(11, 12)<br>• Infections are highly transmissible and often asymptomatic, and early detection relies on regular and comprehensive testing of multiple anatomical sites for those at risk.(11, 13)<br>• Whilst separate testing from these three anatomical sites is preferable, there is additional cost associated with separately testing three sites, which is important to consider especially in low to middle income countries where the cost of nucleic acid amplification test (NAAT) is a major limitation.<br>• The pooling of specimens from multiple anatomical sites from a single individual has been investigated by several studies.(14-16) Currently, there is no clear consensus whether pooling has adequate sensitivity to be used as a detection tool in at-risk populations. | |

**Certainty of the evidence of test accuracy**
**What is the overall certainty of the evidence of test accuracy?**

| RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|

## Chlamydia

| | |
|---|---|
| **Sensitivity** | 0.93 (95% CI: 0.91 to 0.95) |
| **Specificity** | 0.99 (95% CI: 0.99 to 1.00) |

| **Prevalences** | 0% | 10% | 20% |
|---|---|---|---|

| Outcome | № of studies (№ of patients) | Study design | Factors that may decrease certainty of evidence | | | | | Effect per 1,000 patients tested | | | Test accuracy CoE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | pre-test probability of 0% | pre-test probability of 10% | pre-test probability of 20% | |
| **True positives** (patients with chlamydia) | 14 studies 5891patients | cross-sectional (cohort type accuracy study) | serious[a] | not serious | not serious | not serious | none | 0 (0 to 0) | 93 (91 to 95) | 186 (181 to 190) | ⊗⊗⊗◯ MODERATE |
| **False negatives** (patients incorrectly classified as not having chlamydia) | | | | | | | | 0 (0 to 0) | 7 (5 to 9) | 14 (10 to 19) | |
| **True negatives** (patients without chlamydia) | 14 studies 5891 patients | cross-sectional (cohort type accuracy study) | serious[a] | not serious | not serious | not serious | none | 994 (990 to 996) | 895 (891 to 896) | 795 (792 to 797) | ⊗⊗⊗◯ MODERATE |
| **False positives** (patients incorrectly classified as having chlamydia) | | | | | | | | 6 (4 to 10) | 5 (4 to 9) | 5 (3 to 8) | |

***Explanations***

[a] Most studies had patient selection bias and some studies had potential for flow and timing bias.

| RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|

- If you tested 1000 people with a background prevalence of 10% for chlamydia, switching from single-site testing to pooled testing will result in 7 missed cases (out of 100 true cases), and 5 people overtreated.
- If you tested 1000 people with a background prevalence of 20% for chlamydia, switching from single-site testing to pooled testing will result in 14 missed cases (out of 200 true cases), and 5 people overtreated.
- The impact of using a pooled test on missed cases and overtreated cases over a range of background prevalence is presented below.

| Prevalence | Sensitivity | Specificity | PPV | NPV | Number of cases | Missed cases | False Positive (Overtreated) |
|---|---|---|---|---|---|---|---|
| 0.05 | 0.931 | 0.994 | 0.891 | 0.996 | 50 | 3 | 6 |
| 0.1 | 0.931 | 0.994 | 0.945 | 0.992 | 100 | 7 | 5 |
| 0.15 | 0.931 | 0.994 | 0.965 | 0.988 | 150 | 10 | 5 |
| 0.2 | 0.931 | 0.994 | 0.975 | 0.983 | 200 | 14 | 5 |
| 0.25 | 0.931 | 0.994 | 0.981 | 0.977 | 250 | 17 | 5 |
| 0.3 | 0.931 | 0.994 | 0.985 | 0.971 | 300 | 21 | 4 |
| 0.35 | 0.931 | 0.994 | 0.988 | 0.964 | 350 | 24 | 4 |
| 0.4 | 0.931 | 0.994 | 0.990 | 0.956 | 400 | 28 | 4 |
| 0.45 | 0.931 | 0.994 | 0.992 | 0.946 | 450 | 31 | 3 |
| 0.5 | 0.931 | 0.994 | 0.994 | 0.935 | 500 | 35 | 3 |
| 0.55 | 0.931 | 0.994 | 0.995 | 0.922 | 550 | 38 | 3 |
| 0.6 | 0.931 | 0.994 | 0.996 | 0.906 | 600 | 41 | 2 |
| 0.65 | 0.931 | 0.994 | 0.997 | 0.886 | 650 | 45 | 2 |
| 0.7 | 0.931 | 0.994 | 0.997 | 0.861 | 700 | 48 | 2 |
| 0.75 | 0.931 | 0.994 | 0.998 | 0.828 | 750 | 52 | 2 |
| 0.8 | 0.931 | 0.994 | 0.998 | 0.783 | 800 | 55 | 1 |
| 0.85 | 0.931 | 0.994 | 0.999 | 0.718 | 850 | 59 | 1 |
| 0.9 | 0.931 | 0.994 | 0.999 | 0.615 | 900 | 62 | 1 |
| 0.95 | 0.931 | 0.994 | 1.000 | 0.431 | 950 | 66 | 0 |
| 1 | 0.931 | 0.994 | 1.000 | 0.000 | 1000 | 69 | 0 |

PPV = positive predictive value

NPV = negative predictive value

| RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|

## Gonorrhoea

| | |
|---|---|
| **Sensitivity** | 0.94 (95% CI: 0.91 to 0.96) |
| **Specificity** | 1.00 (95% CI: 0.99 to 1.00) |

| **Prevalences** | 0% | 10% | 20% |
|---|---|---|---|

| Outcome | № of studies (№ of patients) | Study design | Factors that may decrease certainty of evidence | | | | | Effect per 1,000 patients tested | | | Test accuracy CoE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Indirectness | Inconsistency | Imprecision | Publication bias | pre-test probability of 0% | pre-test probability of 10% | pre-test probability of 20% | |
| **True positives** (patients with gonorrhoea) | 13 studies 6565 patients | cross-sectional (cohort type accuracy study) | serious[a] | not serious | serious[b] | not serious | none | 0 (0 to 0) | 94 (91 to 96) | 188 (182 to 193) | ⊗⊗◯◯ LOW |
| **False negatives** (patients incorrectly classified as not having gonorrhoea) | | | | | | | | 0 (0 to 0) | 6 (4 to 9) | 12 (7 to 18) | |
| **True negatives** (patients without gonorrhoea) | 13 studies 6565 patients | cross-sectional (cohort type accuracy study) | serious[a] | not serious | not serious | not serious | none | 996 (991 to 998) | 896 (892 to 898) | 797 (793 to 798) | ⊗⊗⊗◯ MODERATE |
| **False positives** (patients incorrectly classified as having gonorrhoea) | | | | | | | | 4 (2 to 9) | 4 (2 to 8) | 3 (2 to 7) | |

***Explanations***

[a] Most studies (n=13) had patient selection bias and 5 studies had potential for flow and timing bias.

[b] Lower sensitivity noted in 4 studies for pharyngeal gonorrhoea

| RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|

- If you tested 1000 people with a background prevalence of 10% for gonorrhoea, switching from single-site testing to pooled testing will result in 6 missed cases (out of 100 true cases), and 4 people overtreated.
- If you tested 1000 people with a background prevalence of 20% for gonorrhoea, switching from single-site testing to pooled testing will result in 12 missed cases (out of 200 true cases), and 3 people overtreated.
- The impact of using pooled samples on missed cases and overtreated cases over a range of background prevalence is presented below.

| Prevalence | Sensitivity | Specificity | PPV | NPV | Number of cases | Missed cases | False Positive (Overtreated) |
|---|---|---|---|---|---|---|---|
| 0.05 | 0.941 | 0.996 | 0.925 | 0.997 | 50 | 3 | 4 |
| 0.1 | 0.941 | 0.996 | 0.963 | 0.993 | 100 | 6 | 4 |
| 0.15 | 0.941 | 0.996 | 0.976 | 0.990 | 150 | 9 | 3 |
| 0.2 | 0.941 | 0.996 | 0.983 | 0.985 | 200 | 12 | 3 |
| 0.25 | 0.941 | 0.996 | 0.987 | 0.981 | 250 | 15 | 3 |
| 0.3 | 0.941 | 0.996 | 0.990 | 0.975 | 300 | 18 | 3 |
| 0.35 | 0.941 | 0.996 | 0.992 | 0.969 | 350 | 21 | 3 |
| 0.4 | 0.941 | 0.996 | 0.994 | 0.962 | 400 | 24 | 2 |
| 0.45 | 0.941 | 0.996 | 0.995 | 0.954 | 450 | 27 | 2 |
| 0.5 | 0.941 | 0.996 | 0.996 | 0.944 | 500 | 30 | 2 |
| 0.55 | 0.941 | 0.996 | 0.997 | 0.932 | 550 | 32 | 2 |
| 0.6 | 0.941 | 0.996 | 0.997 | 0.918 | 600 | 35 | 2 |
| 0.65 | 0.941 | 0.996 | 0.998 | 0.901 | 650 | 38 | 1 |
| 0.7 | 0.941 | 0.996 | 0.998 | 0.879 | 700 | 41 | 1 |
| 0.75 | 0.941 | 0.996 | 0.999 | 0.849 | 750 | 44 | 1 |
| 0.8 | 0.941 | 0.996 | 0.999 | 0.808 | 800 | 47 | 1 |
| 0.85 | 0.941 | 0.996 | 0.999 | 0.749 | 850 | 50 | 1 |
| 0.9 | 0.941 | 0.996 | 1.000 | 0.652 | 900 | 53 | 0 |
| 0.95 | 0.941 | 0.996 | 1.000 | 0.470 | 950 | 56 | 0 |
| 1 | 0.941 | 0.996 | 1.000 | 0.000 | 1000 | 59 | 0 |

PPV = positive predictive value

NPV = negative predictive value

| DESIRABLE EFFECTS<br>How substantial are the desirable anticipated effects? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Single site comparator<br>• DTA data showed reduced sensitivity<br>No testing comparator<br>• Large (based on assumption of comparator) | • Multisite pooled testing has high sensitivity and specificity compared to single site testing.<br>• Our systematic review used 15 estimates from 14 studies for the meta-analysis with data from 5891 patients. For multisite pooled testing **for chlamydia**, we found the combined sensitivity[1] was 93.1% [95% confidence intervals (CI): 90.5-95.0, *I2*=43.3, p<0.001], and combined specificity[2] was 99.4% [95% CI:99.0-99.6, *I2*=52.9, p<0.001].<br>• We used 14 estimates from 13 studies for the meta-analysis with data from 6565 patients. For multisite pooled testing **for gonorrhoea**, we found the combined sensitivity[1] was 94.1% [95% CI: 90.9-96.3, *I2*=68.4, p<0.001], and pooled specificity[2] was 99.6% [99.1-99.8, *I2*=83.6, p<0.001].<br>• Receiving an aetiological diagnosis (rather than relying on syndromic management) means that appropriate antibiotics can be given to patients<br>• Pooled testing encourages multisite STI screening which is more effective in detecting CT/NG infections than the single-site testing in which many extragenital infections would be missed(17, 18)<br>• By expanding the screening coverage and ensuring multisite pooled testing among relevant populations, pooling has the potential to limit the STI pandemic and potentially reduce HIV transmission<br>[1] Sensitivity is a measure of how well a test can identify true positives<br>[2] Specificity is a measure of how well a test can identify true negatives | |

| UNDESIRABLE EFFECTS<br>How substantial are the undesirable anticipated effects? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Single site comparator<br>• Small: missing treatment/ over treatment<br>No testing comparator<br>• May be small | • Sensitivity of retesting the same individual samples could be reduced.(19) In a setting with a background prevalence of 10% for chlamydia, 1000 patients tested with multisite pooled testing (instead of single-site testing) would miss 7 cases (out of 100) and result in 5 cases overtreated. In a setting with a background prevalence of 10% for gonorrhoea, 1000 patients tested with multisite pooled testing would miss 6 cases (out of 100) and 4 cases overtreated.<br>• Four studies among MSM provided information specifically on the sensitivity of detecting pharyngeal pathogens using pooled testing versus the standard of care (i.e. testing of individual swabs). Sensitivities for pharyngeal CT of 100% were noted by Badman et al.,(18) Dean et al.,(20) and Thammajaruk et al.(21) However, Sultan et al.(15) reported a 69.2% sensitivity for pharyngeal CT among 1064 MSM in the UK. The authors hypothesise that the lower performance of pooled testing in detecting pharyngeal infections may be due to inadequate swabbing technique in self-sampling or the lower organism loads seen in pharyngeal infection. However, they also reported that most NG infections were pharyngeal, with a sensitivity of 89.1% for pharyngeal gonorrhoea. This discordance requires further investigation in studies appropriately powered to detect the performance of pooled testing at different anatomical sites. There were lower sensitivities for pharyngeal NG in four studies: 78%,(20) 80%,(18) 89%(15) and 93%.(21) The differences in sensitivity were hypothesised to be attributed to the lower bacterial load in the pharynx compared to other anatomic sites.(15, 18, 21) However, this must be balanced by the opportunity to test the pharyngeal site when using multisite pooled testing in settings where pharyngeal sampling is not routinely performed because of cost. | |

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | • Multisite pooled testing will not provide site-specific information without retesting individuals, which may have previously limited site-specific treatment choices.(15, 17, 19, 22-24) However, WHO recommends the same treatment for genital and extra-genital chlamydia/gonorrhoea meaning that this is no longer a concern. | |
| **CERTAINTY OF EVIDENCE<br>What is the overall certainty of the evidence of effects?** | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Single site comparator<br>• Moderate (test accuracy)<br>No testing comparator<br>• Low (indirect - LMIC, key population group) | • There is certainty regarding the high accuracy of multisite pooled testing because studies had a low risk of bias, there was no publication bias, and although there was moderate heterogeneity, the confidence intervals around the estimates were not wide<br>• Although different methods of pooling were used across the studies (related to flow and timing i.e. different order of pooling sample, different volumes of urine used), the consistently high accuracy of multisite pooled testing despite diverse methodologies of pooling suggest that accuracy was not significantly impacted by the method of pooling.<br>• The studies were predominantly conducted in high-income countries (82.6%, 14/17) and MSM were the most frequently studied population (70.6%, 12/17).<br>• The majority of studies included both clinician and self-collected samples (29.4%, 5/17), followed by self-collected samples (23.5%, 4/17) and health provider collected samples (11.8%, 2/17).<br>• Meta-regression analyses did not show any significant impact on the accuracy of multisite pooled testing according to study population (MSM vs. non-MSM), study population size (<100 vs. >100), country-income level, sample collection (self-collected vs. clinician-collected) or publication year (Before 2020 vs. 2020 or after). | |
| **VALUES<br>Is there important uncertainty about or variability in how much people value the main outcomes?** | | |
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Possibly important uncertainty or variability | • Patients find the testing of chlamydia/gonorrhoea (including self-sampling) to be acceptable.(15, 25) Sultan *et al.* showed most participants found it easy to collect both anorectal and pharyngeal samples (93% and 89%, respectively), and the majority (91%) were confident to take self-collected samples.(15) Similarly, almost all participants (≥97%) in Chernesky's study found steps to self-collect vaginal swabs easy to follow after receiving visual and verbal instructions in the clinic.(25)<br>WHO also commissioned research conducted by global key population networks (MPact and NSWP) that showed an overall willingness among participants to provide and pool samples from 3 anatomic sites (pharynx, urethra, anus).<br>• Evidence from all 6 WHO regions<br>• Participants in agreement with sample pooling, particularly if method would yield more accurate results<br>• Cost-saving was not raised as a factor influencing preferences | Note: this question was only included in the interview/focus group discussion guides of MPact and NSWP. For NSWP participants, only male and transgender sex workers were asked this question. |

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | • MSM (from the MPact network) noted that pooled sampling from 3 anatomic sites could mitigate stigma surrounding anal testing and eliminate the need for health care workers to ask about specific sexual practices. This finding was particularly strong in Africa and the E. Mediterranean region.<br>• MSM (from MPact network) expressed concerns surrounding use of pooled data and confidentiality of data. These concerns were not based on biomedical rationale, underscoring participants' lack of understanding about what pooled sampling may reveal about a person's sexual practices.<br>• Several participants from the NSWP network (from the Americas region) were not willing to have samples collected and pooled due to lack of training of health care workers surrounding this method and lack of information available to sex workers. Although not stated by participants, it can be presumed that single-site screening is a more widespread and established method, with which both health care providers and sex workers would be more familiar.<br>• Participants from both networks were unfamiliar with pooled sampling of STIs, indicating a need for more information on this method's purpose, accuracy, and potential risk. | |

**BALANCE OF EFFECTS**
**Does the balance between desirable and undesirable effects favor the intervention or the comparison?**

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| Favours intervention | | |

| Benefits | Harms |
|---|---|
| Cost savings (reduce cost by a third to two-thirds) | Small numbers of missed cases (5/100 for chlamydia, 6/100 for gonorrhoea) and overtreated cases (5 for chlamydia, 4 for gonorrhoea) compared to single-site testing in a population with 10% background prevalence. |
| Increased test coverage (especially to test more asymptomatic individuals at risk for STIs) | Some uncertainty for sensitivity to detect pharyngeal NG |
| High sensitivity / specificity | No site-specific information without retesting |
| Minimizes risk of not identifying extra-genital STIs | |
| Valued by the community/patients | |
| Self-sampling (which is highly acceptable) did not affect the accuracy of multisite pooled testing | |

| RESOURCES REQUIRED<br>How large are the resource requirements (costs)? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Moderate to large savings if in place and/or integration with other testing; large costs if investment required, varies by setting. | • Sultan *et al.*(15) conducted a study of 1,064 MSM attending UK sexual health clinics and hospital sites between October 2012 and August 2013. Whilst they acknowledged that the costs of each assay varied according to different laboratories, they proposed that pooled testing offers cost savings of up to two-thirds of the costs of the assays alone, as well as savings in consumables, processing time, and clinical pathway efficacy.<br>• Verougstraete *et al.*(17) conducted a prospective study between February 2018 and July 2019 involving 501 female sex workers in Belgium. Their study demonstrated a 35% decrease in reagent costs and lab technician time when using pooled testing. This was calculated using the obtained prevalence of 6.5% and 3.5% for CT and NG, respectively.<br>• De Baetselier *et al.*(24) assessed the efficacy of pooled testing among 497 MSM in four West African countries. They demonstrated a 56% decrease in costs, in which un-pooling of triple-site pooling was only undertaken when the pooled sample result was invalid. | |

| CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES<br>What is the certainty of the evidence of resource requirements (costs)? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| No included studies | | |

| COST EFFECTIVENESS<br>Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Favours intervention, probably favours intervention, some uncertainty | • We identified one cost-effectiveness study by Wilson *et al.*(26) of MSM attending sexual health clinics in the UK. They reported that using a willingness to pay threshold of £60 per person tested, pooled testing had a 100% probability of being cost-effective. Compared with individually analysed samples, pooled testing saved £13.37 to £18.22 per individual tested depending on the symptom status or population group (MSM, women). | |

| EQUITY<br>What would be the impact on health equity? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Increased, Probably increased, some uncertainty | • Seven studies consistently concluded that multisite pooled testing could result in more people tested.(17-20, 23, 24, 27)<br>• One study highlighted this was important to increase testing among asymptomatic individuals in low- and middle-income countries, including multisite pooled testing for PrEP users.(24) | |

| ACCEPTABILITY<br>Is the intervention acceptable to key stakeholders? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Probably yes, some uncertainty | • Shaw *et al.* reported that 84% (41/49) of sexual health clinicians in England considered the most significant benefit of pooling was cost savings.(23)<br>• The greatest barriers were lack of national guidance, loss of infection site information, and a perceived reduction in sensitivity or specificity.(23) In addition, most (77%, 40/52) clinicians requested more validation studies on the diagnostic accuracy, 75% (39/52) wanted clinical guidelines of pooling and 48% (25/52) of clinicians required further cost analysis. | |

| FEASIBILITY<br>Is the intervention feasible to implement? | | |
|---|---|---|
| **JUDGEMENT** | **RESEARCH EVIDENCE** | **ADDITIONAL CONSIDERATIONS** |
| Yes, probably yes, may vary | • No study reported any issues related to the feasibility to combine samples for multisite pooled testing. This included studies from low- and middle-income countries,(21, 24, 28) those that used self-collected samples(14, 15, 17-19, 24-27, 29-31) and those with different timing of pooling after the sample collection (immediately up to 3 days). | |

***References***


1. World Health Organisation. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. World Health Organisation; 2021.
2. Patton ME, Kidd S, Llata E, Stenger M, Braxton J, Asbel L, et al. Extragenital gonorrhea and chlamydia testing and infection among men who have sex with men--STD Surveillance Network, United States, 2010-2012. Clin Infect Dis. 2014;58(11):1564-70.
3. Torrone EA, Morrison CS, Chen PL, Kwok C, Francis SC, Hayes RJ, et al. Prevalence of sexually transmitted infections and bacterial vaginosis among women in sub-Saharan Africa: An individual participant data meta-analysis of 18 HIV prevention studies. PLoS Med. 2018;15(2):e1002511.
4. Chow EPF, Grulich AE, Fairley CK. Epidemiology and prevention of sexually transmitted infections in men who have sex with men at risk of HIV. The Lancet HIV. 2019;6(6):e396-e405.
5. World Health Organization. Global health sector strategy on Sexually Transmitted Infections 2016-2021 [Available from: http://apps.who.int/iris/bitstream/10665/246296/1/WHO-RHR-16.09-eng.pdf?ua=1.

6. Werner RN, Gaskins M, Nast A, Dressler C. Incidence of sexually transmitted infections in men who have sex with men and who are at substantial risk of HIV infection - A meta-analysis of data from trials and observational studies of HIV pre-exposure prophylaxis. PLoS One. 2018;13(12):e0208107.
7. Cohen MS, Hoffman IF, Royce RA, Kazembe P, Dyer JR, Daly CC, et al. Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. AIDSCAP Malawi Research Group. Lancet. 1997;349(9069):1868-73.
8. Unemo M, Jensen JS. Antimicrobial-resistant sexually transmitted infections: gonorrhoea and Mycoplasma genitalium. Nat Rev Urol. 2017;14(3):139-52.
9. Cristillo AD, Bristow CC, Torrone E, Dillon JA, Kirkcaldy RD, Dong H, et al. Antimicrobial Resistance in Neisseria gonorrhoeae: Proceedings of the STAR Sexually Transmitted Infection-Clinical Trial Group Programmatic Meeting. Sex Transm Dis. 2019;46(3):e18-e25.
10. Barbee LA, Dombrowski JC, Kerani R, Golden MR. Effect of nucleic acid amplification testing on detection of extragenital gonorrhea and chlamydial infections in men who have sex with men sexually transmitted disease clinic patients. Sex Transm Dis. 2014;41(3):168-72.
11. van Liere GA, van Rooijen MS, Hoebe CJ, Heijman T, de Vries HJ, Dukers-Muijrers NH. Prevalence of and Factors Associated with Rectal-Only Chlamydia and Gonorrhoea in Women and in Men Who Have Sex with Men. PLoS One. 2015;10(10):e0140297.
12. Gunn RA, O'Brien CJ, Lee MA, Gilchick RA. Gonorrhea screening among men who have sex with men: value of multiple anatomic site testing, San Diego, California, 1997-2003. Sex Transm Dis. 2008;35(10):845-8.
13. Australasian Society for HIV Medicine. The Australasian STI Management Guidelines ASHM; 2020.
14. Bristow CC, Mehta SR, Hoenigl M, Little SJ. The performance of pooled 3-anatomic-site chlamydia and gonorrhea testing. Topics in Antiviral Medicine. 2020;28 (1):398-9.
15. Sultan B, White JA, Fish R, Carrick G, Brima N, Copas A, et al. The "3 in 1" Study: Pooling Self-Taken Pharyngeal, Urethral, and Rectal Samples into a Single Sample for Analysis for Detection of Neisseria gonorrhoeae and Chlamydia trachomatis in Men Who Have Sex with Men. Journal of Clinical Microbiology. 2016;54(3):650-6.
16. Wilson J, Wallace H, Loftus-Keeling M, Ward H, Hulme C, Wilcox M. Clinician-taken extra-genital samples for gonorrhoea and chlamydia in women and msm compared with self-taken samples analysed separately and self-taken pooled samples. Sexually Transmitted Infections. 2017;93 (Supplement 2):A26.
17. Verougstraete N, Verbeke V, De Canniere AS, Simons C, Padalko E, Coorevits L. To pool or not to pool? Screening of Chlamydia trachomatis and Neisseria gonorrhoeae in female sex workers: pooled versus single-site testing. Sexually Transmitted Infections. 2020;96(6):417-21.
18. Badman SG, Bell SFE, Dean JA, Lemoire J, Coffey L, Debattista J, et al. Reduced sensitivity from pooled urine, pharyngeal and rectal specimens when using a molecular assay for the detection of chlamydia and gonorrhoea near the point of care. Sexual Health. 2020;17(1):15-21.
19. Speers DJ, Chua IJ, Manuel J, Marshall L. Detection of Neisseria gonorrhoeae and Chlamydia trachomatis from pooled rectal, pharyngeal and urine specimens in men who have sex with men. Sexually Transmitted Infections. 2018;94(4):293-7.
20. Dean JA, Bell SFE, Coffey L, Debattista J, Badman S, Redmond AM, et al. Improved sensitivity from pooled urine, pharyngeal and rectal specimens when using a molecular assay for the detection of chlamydia and gonorrhoea near point of care. Sexually Transmitted Infections. 2020;13:13.
21. Thammajaruk N, Promthong S, Posita P, Chumseng S, Nampaisan O, Srivachiraroj P, et al. Pooled pharyngeal, rectal and urine samples for the Point-of-Care detection of Chlamydia trachomatis and Neisseria gonorrhoeae by lay-providers in Key Population-Led Health Services in Thailand. Journal of the International Aids Society. 2020;23:115-6.
22. Durukan D, Read TRH, Bradshaw CS, Fairley CK, Williamson DA, De Petra V, et al. Pooling Pharyngeal, Anorectal, and Urogenital Samples for Screening Asymptomatic Men Who Have Sex with Men for Chlamydia trachomatis and Neisseria gonorrhoeae. Journal of Clinical Microbiology. 2020;58(5):23.
23. Shaw J, Saunders JM, Hughes G. Attitudes to, and experience of, pooled sampling for sexually transmitted infection testing: a web-based survey of English sexual health services. International Journal of STD & AIDS. 2018;29(6):547-51.
24. De Baetselier I, Vuylsteke B, Yaya I, Dagnra A, Diande S, Mensah E, et al. To pool or not to pool samples for sexually transmitted infections detection in men who have sex with men? An evaluation of a new pooling method using the genexpert instrument in West Africa. Sexually Transmitted Diseases. 2020;47(8):556-61.
25. Chernesky M, Jang D, Martin I, Arias M, Shah A, Smieja M, et al. Mycoplasma genitalium, Chlamydia trachomatis, and Neisseria gonorrhoeae Detected With Aptima Assays Performed on Self-Obtained Vaginal Swabs and Urine Collected at Home and in a Clinic. Sexually Transmitted Diseases. 2019;46(9):e87-e9.
26. Wilson JD, Wallace HE, Loftus-Keeling M, Ward H, Davies B, Vargas-Palacios A, et al. Swab-yourself trial with economic monitoring and testing for infections collectively (SYSTEMATIC): Part 2. A diagnostic accuracy, and cost-effectiveness, study comparing rectal, pharyngeal and urogenital samples analysed individually, versus as a pooled specimen, for the diagnosis of gonorrhoea and chlamydia. Clinical Infectious Diseases. 2020;12:12.

27. De Baetselier I, Osbak KK, Smet H, Kenyon CR, Crucitti T. Take three, test one: a cross-sectional study to evaluate the molecular detection of Chlamydia trachomatis and Neisseria gonorrhoeae in pooled pharyngeal, anorectal and urine samples versus single-site testing among men who have sex with men in Belgium. Acta Clinica Belgica. 2020;75(2):91-5.

28. Romyco I, Umboh L, Erari S, Wignall S. Performance of 3-in-1 pooled samples from anal, rectal, and throat of genexpert CT/NG in Bali, Indonesia. Sexually Transmitted Infections. 2019;95 (Supplement 1):A104.

29. Ando N, Mizushima D, Watanabe K, Takano M, Shiojiri D, Uemura H, et al. Modified self-obtained pooled sampling to screen for Chlamydia trachomatis and Neisseria gonorrhoeae infections in men who have sex with men. Sexually Transmitted Infections. 2020;20:20.

30. Singh S, Hopkins M, Sarner L. High prevalence of extragenital chlamydia trachomatis (CT) in heterosexual women: Validation of pooled samples. Sexually Transmitted Infections. 2019;95 (Supplement 1):A217-A8.

31. Thielemans E, Wyndham-Thomas C, Henrard S, De Vleeschouwer A, Steensels D, Montesinos I, et al. Screening for Chlamydia trachomatis and Neisseria gonorrhoeae Infections in Men Who Have Sex With Men: Diagnostic Accuracy of Nucleic Acid Amplification Test on Pooled Urine, Anorectal, and Pharyngeal Specimens. Sexually Transmitted Diseases. 2018;45(3):195-8.

## Summary of Guideline Development Group judgements

| Question | Judgement | |
|---|---|---|
| **1. Is the problem a priority?** | Yes | |
| | **Single site comparator** | **No testing comparator** |
| **2. How substantial are the Benefits?** | DTA data showed reduced sensitivity | Large (based on assumption of comparator) |
| **3. How substantial are the Harms?** | Small: missing/over treatment | May be small |
| **4. What is the overall certainty of the evidence?** | Moderate (test accuracy) | Low (indirect LMIC, KP) |
| **5. What is the balance between Benefits & Harms?** | Favours intervention | |
| **6. How do people value pooling sampling?** | Possibly important uncertainty or variability | |
| **7. How large are the resource requirements?** | Moderate to large savings if in place and/or integration with other testing, Large costs if investment required, varies | |
| **8. What is the certainty of evidence for the costs?** | Not applicable | |
| **9. Is pooling cost-effective?** | Favours intervention, Probably favours intervention, some uncertainty | |
| **10. What would the impact be on health equity?** | Increased, Probably increased, some uncertainty | |
| **11. Is pooling acceptable to all stakeholders?** | Probably yes, some uncertainty | |
| **12. Is pooling feasible to implement?** | Yes, probably yes, may vary | |
| **Recommendation** | In favour (conditional, low certainty) | |


World Health
Organization


9789240053465
9 789240 053465