Comprehensive needle and syringe program and opioid agonist therapy reduce HIV and HCV acquisition among people who inject drugs in different settings: a meta-analysis of emulated trials

Maria Prins
Public Health Service (GGD) of Amsterdam
Amsterdam UMC, Amsterdam
the Netherlands
Introduction
Harm reduction programs for people who inject drugs (PWID) in Amsterdam

1979: Methadone bus
Opiate Agonist Therapy (OAT)

1984: Needle and Syringes Program (NSP)
by Junkiebond (NGO)
Declining HCV and HIV incidence and numbers of PWID

van Santen et al, Addiction 2021; de Vos et al, Addiction 2013
Full participation in harm reduction programmes is associated with decreased risk for human immunodeficiency virus and hepatitis C virus: evidence from the Amsterdam Cohort Studies among drug users

Charlotte Van Den Berg, Colette Smit, Giel Van Brussel, Roel Coutinho & Maria Prins

Department of Human Retrovirology, Center for Infection and Immunity Amsterdam (CINIMA), Academic Medical Center, Amsterdam, the Netherlands; Cluster Infectious Diseases, Department of Research, Amsterdam Health Service, Amsterdam, the Netherlands; Cluster Social and Mental Healthcare, Amsterdam Health Service, Amsterdam, the Netherlands; National Institute for Public Health and the Environment, Center for Infectious Disease Control, Bilthoven, the Netherlands; and Department of Internal Medicine, Division of Infectious Diseases, Tropical Medicine and AIDS, CINIMA, Academic Medical Center, Amsterdam, the Netherlands

van den Berg et al, Addiction 2007; de Vos et al, Addiction 2013
Background current study
Weak evidence for effect harm reduction on infection risk?

Observational cohort studies:
- Insufficient adjustment for confounding and selection bias

Randomized controlled trial would provide the strongest possible evidence for a causal effect of harm reduction on infection risk
- Unethical to include an arm without harm reduction programs as the benefits of these programs across a range of outcomes are recognized
Harm reduction programs for PWID in Amsterdam revisited
Re-use of cohort data using novel methods for causal inference

**Novel method:** Emulated trial using data from observational studies

**Key finding:** Harm reduction works in Amsterdam!
Comprehensive NSP and OAT reduced risk of acquisition of
- HIV by 45%
- HBV by 72%
- HCV by 84%

van Santen, Addiction 2021
Background: Evidence from one setting sufficient?  
Re-use of cohort data from 3 settings

- The Netherlands, Canada and Australia were all early adopters of harm reduction for PWID

- Their respective HIV and hepatitis C (HCV) epidemics and populations of PWID differ e.g.
  - HIV never successfully introduced among PWID in Australia
  - Drug consumptions rooms were available much earlier in the Netherlands than in Australia and Canada
  - Coverage of harm reduction components differed between countries
  - Different market for illicit drugs
Objective

Determine the effect of comprehensive NSP/OAT participation on HIV and HCV infection risk using observational cohort data from Vancouver, Amsterdam and Melbourne
Methods: study population and data

PWID at risk of infection from three cohort studies

ACS
Amsterdam Cohort Studies

VIDUS
The Vancouver Injection Drug Users Study

SuperMIX
The Melbourne Injecting Drug User Cohort Study
## Study design: Emulating a target trial

<table>
<thead>
<tr>
<th>Protocol component</th>
<th>Target trial</th>
<th>Emulated trial</th>
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<tbody>
<tr>
<td><strong>Eligibility</strong></td>
<td>• HIV or HCV antibody negative</td>
<td>Same as for the target trial</td>
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<tr>
<td></td>
<td>• Recent injecting</td>
<td><em>Opioid use disorder defined as any recent opioid use</em></td>
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<tr>
<td></td>
<td>• Opioid use disorder</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ≥18 years old</td>
<td></td>
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<tr>
<td><strong>Follow up</strong></td>
<td>Study enrolment (baseline) until the visit at which the participant deviated</td>
<td>Same as for the target trial</td>
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<tr>
<td></td>
<td>from their initial baseline intervention strategy, outcome occurrence, loss</td>
<td>*Baseline was defined as the first visit the participant met the eligibility</td>
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<tr>
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<td>to follow-up, administrative censoring date or 2.5 years after baseline.</td>
<td>criteria, had an HIV or HCV test result and complete data was available.</td>
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<tr>
<td><strong>Intervention strategies</strong></td>
<td>Three intervention arms:</td>
<td>Two intervention arms:</td>
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<tr>
<td></td>
<td>1) No NSP/OAT</td>
<td>1) No and partial NSP/OAT combined</td>
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<td></td>
<td>2) Partial NSP/OAT: &lt;100% NSP coverage and/or no current OAT among</td>
<td>2) Comprehensive NSP/OAT</td>
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<tr>
<td></td>
<td>participants reporting current injecting.</td>
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<td></td>
<td>3) Comprehensive NSP/OAT: 100% coverage of NSP and current OAT among</td>
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<tr>
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<td>participants reporting recent injecting or, current OAT only when</td>
<td></td>
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<tr>
<td></td>
<td>reporting no current injecting.</td>
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<tr>
<td><strong>Intervention assignment</strong></td>
<td>Random assignment</td>
<td>Individuals were classified to each intervention strategy based on the</td>
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<td>observed data. We adjusted for baseline and time-varying confounders.</td>
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<td><strong>Casual contrast</strong></td>
<td>Intention to treat and per protocol</td>
<td>Observational analogue of per-protocol analysis</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>HIV, HCV or HBV seroconversion</td>
<td>Same as for the target trial</td>
</tr>
<tr>
<td><strong>Statistical analyses</strong></td>
<td>Cox-proportional hazard models. Using inverse-probability weights (IPW)</td>
<td>Separate for each cohort: marginal structural models using a sequential</td>
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<tr>
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<td>to adjust for baseline and time-varying confounders associated with</td>
<td>trial emulation approach, adjusting for confounders and loss to follow up.</td>
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<td>baseline participation adherence in the per-protocol analysis. For both the</td>
<td>Combing data from the cohorts: pooled hazard ratios (HR) and 95%CI were</td>
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<td>ITT and per-protocol analysis include IPW to adjust for potential lost to</td>
<td>calculated using random-effect models.</td>
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<td>follow up.</td>
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Results: Complete vs no/partial NSP/OAT participation
Conclusion

When applying a target trial approach to infer causality from observational data, we demonstrated that comprehensive NSP/OAT led to a **substantial reduction of HIV and HCV acquisition** compared to no/partial participation in different settings of high-income countries.

These findings coupled with the fact that this intervention is associated with reductions in drug use, criminal activity and mortality, and engagement in care – reinforce the critical role of access to harm reduction programs – suggest that WHO should emphasize access to comprehensive NSP and OAT rather than each component separately.

Given that most countries lack access to comprehensive NSP/OAT, and global HCV and HIV elimination is unlikely to be reached by 2030, **increased coverage of these key interventions will be vital to preventing new infections**.
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dvsanten@ggd.amsterdam.nl  @GGDAmsID