



European Monitoring Centre
for Drugs and Drug Addiction

DRID Guidance Module

METHODS OF BIO-BEHAVIOURAL SURVEYS ON HIV AND VIRAL HEPATITIS IN PEOPLE WHO INJECT DRUGS — A SHORT OVERVIEW

**EMCDDA DRID Bio-Behavioural Methods Module
VERSION 1.0**

27/01/2014

**EMCDDA Drug Related Infectious Diseases
(DRID) Monitoring Guidance Toolkit**

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Acknowledgements:

Substantial input was given by:

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Victor Mravcik, Head of the Czech National Focal Point for Drugs and Drug Addiction Office of the
Government of the Czech Republic

Jesus Maria Garcia Calleja, WHO Geneva

Thanks to other participants of the Advisory Group meeting of 9 October 2012:

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Catharina Matheï, ACHG, KULeuven, Leuven

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We also thank the participants of the DRID meeting 10–11 October 2012 for their valuable contributions.

Recommended citation:

European Monitoring Centre for Drugs and Drug Addiction (2013), *DRID Guidance Module: Methods of bio-behavioural surveys on HIV and viral hepatitis in people who inject drugs — a short overview*, EMCDDA, Lisbon.

I. Introduction

- *Harmonising second generation surveillance among IDUs in Europe*

The aim of this module is to provide guidance in implementation and use of biological and behavioural studies among people who inject drugs (injecting drug users/IDUs) as a tool in routine surveillance at the country and European level.

This could be considered a step towards harmonising and improving the quality of the second generation surveillance among IDUs in Europe. Second generation surveillance for human immunodeficiency virus/ acquired immune deficiency syndrome (HIV/AIDS) is defined as 'the regular, systematic collection, analysis and interpretation of information for use in tracking and describing changes in the HIV/AIDS epidemic over time. Second generation surveillance for HIV/AIDS also gathers information on risk behaviours, using them to warn of or explain changes in levels of infection' ⁽¹⁾. For considerations on the framework for second generation surveillance among IDUs in Europe please see the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)'s *DRID protocol* for the implementation of key indicators on drug related infectious diseases (DRIDs) ⁽²⁾. The background will be further explained in a future introduction module of this Toolkit. Information on biological and behavioural indicators can be obtained through pooling and analysis of data collected for other purposes (secondary data sources) or through specifically designed studies. For guidelines on possible sources and utilisation of secondary data please refer to the EMCDDA's *Draft protocol* ⁽²⁾. The topic will be covered also in a future module on prevalence and behavioural data from diagnostic testing, TDI and other registries.

In this module:

Introducing methods for running bio-behavioural surveys among IDUs

Bringing together existing guidelines highlighting IDU specific information

Discussing preferred methods in view to harmonise second generation surveillance of IDUs in Europe

The present module covers studies that are specifically designed to obtain information on seroprevalence of HIV/hepatitis C virus/hepatitis B virus infection in IDUs and/or specific behaviours that are important in the context of these diseases. Whilst acknowledging the role of qualitative studies in understanding behaviours and behavioural changes, this module focuses mainly on quantitative measurements.

- *Existing guidelines*

There are existing documents providing step-by-step guidance on planning and implementation of biological, bio-behavioural and behavioural studies in the framework of second generation surveillance. Those guidelines present the second generation surveillance approaches from different angles, usually underlining their relevance in HIV surveillance, and are not specific for studies among IDUs. Furthermore, most of the guidelines have been designed to serve the needs of both developed and developing countries. In this module we summarise recommended practices that are the most relevant to studies of IDUs, putting them more specifically in a European context. Therefore this module, rather than providing prescriptive detailed guidance for developing a study protocol, aims to allow easy reference to particular topics in other guidelines that are useful in designing biological and behavioural studies among IDUs. The module further aims to provide updated information by including reference to

Key documents:

Draft protocol for the implementation of DRID, EMCDDA and Greek FP 2006 ⁽²⁾

Behavioural surveillance surveys, Family Health International, 2000 ⁽³⁾

Behavioural surveillance toolkit, ECDC, 2010 ⁽⁴⁾

Guidelines on surveillance among populations most at risk for HIV, WHO/UNAIDS, 2011 ⁽⁵⁾

Surveillance of populations at high risk for HIV transmission, CDC/GAP, UCSF, 2010 ⁽⁶⁾.

and summaries of recent methodological developments, practical experience and criticisms on these methods. Moreover, the present module also covers other drug related infections than HIV — in particular hepatitis C virus (HCV) and hepatitis B virus (HBV) — which are not part of existing guidelines.

The references to the key existing documents are given in the box ^(2, 3, 4, 5, 6). These documents are complemented by references to additional guideline documents for specific sections, the recent published literature on studies among IDUs and textbooks. Moreover, the Joint United Nations Programme on HIV/AIDS and the World Health Organization (UNAIDS/WHO) are updating several modules on second generation surveillance, which will be accessible at www.who.int/hiv/strategic/surveillance/en/.

- *Overriding divisions and the use for surveillance purposes*

For the purpose of surveillance, studies among IDUs can be classified as shown in Table 1. Unlinking studying biological markers and behavioural indicators has been recommended by Family Health International (FHI) ⁽³⁾ in order to avoid participation bias in behavioural studies. The results are then linked at population level and presented together. In studies among IDUs there are not many options to run representative unlinked anonymous bio-surveys. Additionally, this could be regarded as missing an opportunity to provide testing and in consequence access to treatment. All existing surveillance guidelines focus on repeated cross-sectional surveys. However, in many European countries there exist cohort studies of drug users that provide important insight into infectious disease risk in this population.

Study settings have a fundamental impact on the study design, logistics and sustainability. It is also not always clear how representative the population accessible in different settings is for the whole drug using population. In the European context, in countries where coverage of services is high, sampling at services might be the method of choice ⁽⁴⁾. Where service coverage is low, chain-referral studies (respondent-driven sampling) or other community-wide methods may result in more representative samples.

This document focuses on bio-behavioural cross-sectional studies, while the choice of settings will depend on the local situation and the aims of the study. Nevertheless, the results may be more likely to be generalisable if combining open service settings (low threshold facilities) with community recruitment.

Definitions:

Behavioural surveillance surveys – cross-sectional, quantitative studies collecting behavioural indicator data.

Biological surveillance surveys – cross-sectional studies in which biological samples are collected and tested. The term is sometimes used to describe case-based reporting of new diagnoses.

Bio-behavioural surveillance surveys — combine collecting biological samples and behavioural indicators from the same individuals

Table 1 — Overriding divisions of studies used in bio-behavioural surveillance.

Categorisation		Description	Comments on use
Type of information collected	Biological (e.g. seroprevalence)	Collect biological markers of infections from target population	Very unusual in IDUs without collecting interview data.
	Behavioural	Collect behavioural indicators from target population	More frequently done. Biological investigations usually left out due to logistical and costs issues.
	Bio-behavioural	Collect linked biological markers and behavioural indicators from target population	Frequently done, combines both types of information.
Epidemiological study type	Cross-sectional	Information collected from a (representative) sample of target population at a single point in time	Frequently done due to relative simplicity.
	Cohort	Members of the target population are observed in time (followed up). Typically outcome (e.g. incidence of disease) is compared among exposed and non-exposed groups.	Infrequently done, despite strong design, due to complexity/costs of following up IDUs over time.
	Case-control	Odds of exposure are compared among cases (e.g. infected) and controls (typically uninfected).	Not very frequent, analysis is relatively similar to cross-sectional.
	Ecological	Average level of exposure and a measure of frequency of outcome are correlated across units such as counties or schools.	Not very frequent due to problems in interpreting results (weaker design). However, may be useful to study population level factors.
Study settings/ sampling frame	Community	Respondents are recruited directly from the community of drug users, either by researcher visiting places where drug users congregate or via other community members.	Frequently done. Provides relatively generalisable data, but at relatively high costs.
	Services (outpatient)	Respondents are recruited from clients/patients of various services for drug users, where they come for specific service but are not expected to stay a full day.	Frequently done due to ease of recruitment. May be less generalisable if services have low coverage.
	Closed settings	Respondents are recruited from settings where they spend at least one full day, such as detoxification wards, stationary rehabilitation centres or prisons.	Frequently done, easier logistics, ethical issues are even more important. May be difficult to generalise to IDUs outside these settings.

II. Steps in planning and implementation of a study

When setting up bio-behavioural, biological or behavioural surveys among IDUs with an objective of serving immediate public health purposes, a number of steps will be relevant prior to research activities in order to ensure proper use of the information generated later on. The steps to be considered are outlined in (3) or (5). They include:

1. Building partnerships:

- Ensure that the plans are in line with the main stakeholder's needs. It is useful to take advantage of existing knowledge and experience. The possible structures that could be contacted include those that will use the results of survey(s), those who potentially could be involved, and those who can help through their expertise or mandate.
- The best collaborations and strongest support for a study can often be obtained when involving stakeholders at a very early stage and allowing them to provide comments and ideas for the study when these can still be easily integrated in the plans (allowing them 'shared ownership').
- Depending on the local situation, these could include governmental agencies, local government, resource planning structures, surveillance structures, infectious disease (HIV, hepatitis) prevention programmes, monitoring and evaluation programmes, clinical services (infectious disease, drug treatment), low threshold services for drug users, local police departments, universities, and also NGOs and community members.
- An agreement should be set up between the stakeholders including the rules of publicising the results, ownership of the data and financial responsibilities of the parties.

2. Assessing the existing evidence on drug using population and infectious disease among drug users:

- The existing information should be reviewed, such as results of surveillance and other monitoring systems (e.g. treatment provision, mortality), on-going public health interventions, police data, previous studies. Qualitative research or rapid assessment (7) might be also useful to get an idea about the organisation of the local drug scene, norms and behaviours.
- Ideally these data will help identify geographical areas where the study should be implemented (e.g. high incidence sites), approximate prevalence of injecting drug use, as well as information determining the choice of the study design and the study logistics, for example existence of an open drug scene, degree of networking among the drug users, coverage of services, etc.
- The legal background should also be reviewed regarding drug use, biological sample collection, conducting studies, data protection and ethical approval.

3. Defining clear objectives:

- Based on the preliminary information collected and public health needs there have to be clearly defined objectives and study questions beginning with fundamental decisions such as if the study is planned as a rapid assessment of the situation, an in-depth analysis of specific problems or a part of a long term monitoring process.
- It should also be clear what are the priorities for information and the main outcome measures/indicators: monitoring trends in disease occurrence (incidence, prevalence), monitor frequency of risk behaviours, monitoring programme coverage, monitoring programme targets or others.
- Depending on the primary study question, consider whether the study should be specifically designed to provide information about any specific subpopulation (e.g. young drug users, female drug users, injecting/non-injecting populations, specific substance users) and if the study should target any specific area (the criteria to select

such sites: incidence of infectious diseases, coverage of services, prevalence of injecting use).

4. Study planning and implementation (further developed in the specific sections):
 - a. Defining the target population.
 - b. Deciding sampling design, constructing sampling frame and calculating sample size.
 - c. Developing the survey protocol including study instruments (questionnaire).
 - d. Training interviewers and identifying pilot survey procedures and instruments.
 - e. Data collection and supervision.
 - f. Data management and analysis.
5. Using the data to improve prevention efforts against drug related infectious diseases:

As the main assumption of surveillance is that the data collected should be used, ways of publicising study results and the target audiences should be planned in advance. Besides the full report there should be appropriately presented information for the community and key messages for the stakeholders.

III. Defining the target population

The target population is the population that the researchers wish to study and refer their results to. Ideally, the recruited sample is representative for the target population and the results of the study can be generalised to the target population. For this reason it may be advisable to explicitly restrict the target population, excluding subgroups that are no longer accessible. For example, surveys among IDUs usually exclude ever-injectors who no longer take drugs.

In the context of blood borne infectious diseases the highest risk is due to unsafe injections and therefore the focus of the surveillance studies usually remains on injecting drug users^(2, 3, 4, 5, 6). Therefore, if the survey includes non-injecting problem drug users then the results should always be presented separately for ever-injectors and never-injectors. Generic definitions are provided in the box. However, the study should define specific inclusion criteria.

The EMCDDA *Draft Protocol*⁽²⁾ distinguishes the following target populations:

- a. Ever-IDUs who are also recent (last 12 months) problem drug users (PDUs).
- b. Recent/current/active (last 4 weeks) IDUs.
- c. Ever-IDUs in the general population (includes ever-IDUs who are not recent PDUs).
- d. Recent (last 12 months) PDUs — always distinguishing ever- and never-IDUs.

Most of the surveillance studies focus on ever-injectors or current injectors as their target group (but only those who still use drugs, i.e. who are still recent PDUs — groups a and b above). The local situation and study aims may justify selecting a subgroup of those based for example on age (e.g. young injectors aged <25 or <30), using specific substances (e.g. opioid injectors), or race/ethnicity/migration status. New injectors, even though an important group, are usually not targeted specifically but are distinguished in the analysis given that they are difficult to recruit separately and would often result in very small sample size.

Relatively less focus has been placed so far on non-injecting drug users (NIDUs). However, there is evidence of a higher prevalence of blood borne infections among NIDUs than among the general population, even if the prevalence will usually be much lower than among IDUs. This is attributed to an increased risk of sexual transmission (high risk sexual behaviours and/or bridging from IDUs), sharing of non-injection paraphernalia or other routes such as tattooing in non-professional settings (e.g. in prisons). A sufficient explanation of this increased prevalence among NIDUs is still to be identified, and to an unknown extent this group may include ever-injectors who do not wish to disclose their injection history^(8, 9). This group may, however, be important subjects of study in situations where prevalence among IDUs is high and when it is suspected that transmission other than through injecting is important (e.g. sexual transmission for HIV or HBV).

For the purpose of surveillance of HIV, HBV, HCV it is usually recommended that studies concentrate on recent/active injectors if they are repeated frequently, in order to monitor change in the population. If the studies are infrequent and it is important to obtain a full picture of the burden of disease in the IDU population it might be better to include all ever-injectors in the drug using population. Including all ever-IDUs in the general population, although in theory ideal, is usually not practical as those who have stopped using drugs would be very difficult to recruit.

The EMCDDA collects prevalence data from ever-injectors; these may be either all ever-IDUs (both active and ex-IDUs) or be limited to the subgroup of active injectors. In terms of comparing prevalence estimates, the choice between ever-IDUs and active injectors often does not make much difference for the resulting prevalence, as in many European countries most active injectors are opioids injectors

Definitions:

Injecting drug use (IDU)

Injecting a psychoactive substance for non-medical purposes.

Includes intravenous injecting, intramuscular injecting or injecting under the skin ('skin popping').

Problem drug use (PDU)

Injecting drug use or long-duration/regular use of opioids, cocaine and/or amphetamines.

who have long injecting careers and remain actively injecting for many years. Similarly, when comparing prevalence from studies that define active injectors as those injecting in the last 12 months, last 6 months or in the last 4 weeks, the resulting prevalence estimates are usually very similar in the case of opioid injectors. This is because opioids injectors are mostly long-term chronic injectors and thus most active injectors who have injected in the last 12 months will also have injected in the last 4 weeks.

Table 2 — Variables commonly used to define target groups.

Subgroup (EMCDDA definition)	Description	When to focus
<i>Drug injecting status</i>		
Ever-injectors (having ever injected in lifetime, even if only once)	<p>Ever-injectors are at risk of being infected with HIV/HCV. Infection could have occurred a long time before the study. Depending on service coverage, a substantial proportion of infections would be already diagnosed.</p> <p>They might still use drugs and remain at increased risk through their sexual networks. They might be a source of infection to others.</p>	<p>Not much known about prevalence of blood-borne viruses among IDUs.</p> <p>High undiagnosed fraction (to monitor efforts to decrease it), burden of disease.</p> <p>Risk of sexual spread to non-IDUs when prevalence is high in ever-IDUs.</p>
Non-injecting PDU (having never injected a psychoactive substance, not even once)	<p>Non-injectors are at risk of transition to injecting and they may have an increased proportion of injectors in their social networks who can act as source.</p>	<p>Settings where injecting levels are low or declining, especially if there is a high prevalence in injectors due to prior epidemics.</p>
<i>Duration of injecting history</i>		
New injectors (first injection less than 2 years ago)	<p>New injectors are at a very high risk for infections. The prevalence among new injectors may form an indicator of incidence. The new injectors might not yet be covered by services.</p>	<p>Low prevalence settings. Settings with high coverage of services.</p> <p>Due to sample size considerations it may be best to differentiate at the level of analysis, e.g. sampling recent IDUs.</p>
<i>Recent injecting</i>		
Current/recent/active injectors (having injected in the last 4 weeks)	<p>Current/recent injectors form networks for the spread of blood-borne viruses. Their behaviours and prevalence in this group will determine injection related spread.</p>	<p>Monitoring of current risk. Impact of services.</p>
<i>Age</i>		
Young injectors (<25 years)	<p>Not as good an indicator for incidence as prevalence in new IDUs, but still a group that concentrates IDUs with shorter injecting careers, often higher risks and potentially less coverage of services.</p>	<p>To study recent developments in the IDU population, e.g. recent trends in new substances.</p>

Substance of choice

Opioid users

Usually the group with the biggest problems and highest prevalence, especially when they combine opioids and stimulants (e.g. injecting both together). This group usually includes those who inject both types of substances. Heroin has historically been the dominant opioid and home-made opiates from poppy straw were also present in some Eastern European countries. Recently, other opioids like illicit buprenorphine or fentanyl have become regionally prevalent.

When the study aims focus around opioids substitution treatment coverage or when purely stimulant injection is not very common.

Stimulant users

Studies interested in stimulant injectors often focus on those who do not also use opioids, i.e. pure stimulant injectors (e.g. amphetamine or methamphetamine injectors). These often have very different social networks and behaviour from opioids users, often including less contact with services. If a study includes both opioid users and stimulant users then in the analysis phase they are usually distinguished (either putting those who use both substances in the opioids users group or distinguishing three groups).

When injecting of stimulants is a significant phenomenon in the country.

Residence

IDU, residents of the area

Those living in the studied area for a specified time period, e.g. 12 month prior to the survey.

Many studies exclude non-residents to better quantify the burden of disease in the area. This also allows better reference to capture-recapture studies estimating the local population size of injectors. In cases where there is a high turnover of population, including non-residents may provide important insights, e.g. in importation risks.

Gender

IDU, females/males

It is uncommon to recruit just one gender.

IV. Defining the sampling frame

A sampling frame is the population from which the sample is actually taken. There should be a well-defined access to this population. Ideally, a list of members of the sampling frame exists, from which the sample can be drawn. The sampling frame population should be a good representation of the target population.

Drug users remain a hard to reach population and each of the potential sampling frames has its drawbacks and is likely to introduce some bias. A common approach is therefore to use different sampling frames in one study (e.g. recruitment from services and on the streets) in order to reduce overall bias when generalising to the full IDU population. Nevertheless, generalisation of the results of one survey among IDUs is always problematic.

The selection of the sampling frame will depend on the target population, on the characteristics of the drug scene/services and on the resources that are available.

Commonly used sampling frames include:

1. Community — Drug users who stay in touch/are networked with other drug users. This could be through either attending specific venues (other than services) or personal networks.
 - Usually the closest to the target population, although may exclude ex-users.
 - Hard to reach, requires specific resource intensive approaches.
2. Clients of outpatient services — Drug users who seek help from a service provider (agency) or are reached by outreach workers. An agency can be defined as a structure that employs staff to enter in direct contact with drug users and provides harm reduction services, general health services, dependency treatment to them in a fixed place, but on an outpatient basis ⁽¹⁰⁾.
 - It will include users who will seek addiction treatment, including opioid substitution treatment (OST) (treatment demand), infectious disease testing or routine health check-ups, harm reduction services such as needle and syringe programmes (NSPs), drug consumption facilities, social services (drop-in centres, emergency shelters).
 - This frame offers the advantage of controlled study site conditions (e.g. allowing biological sample collection, increasing the safety of interviewers).
 - Services are not advisable as a single sampling frame in cases where there is low service coverage of the target population or when certain subpopulations are known not to be in contact with the service (e.g. stimulant users are not likely to be in contact with OST).

Types of services/service providers:

Service providers may operate differently in different countries and therefore service based sampling can reach different subgroups of drug users. To increase comparability of service-based sampling frames the following characteristics can be taken into account:

- Type of service provided (impact on efficiency of recruitment, social standing of the respondents, stigmatisation issues):
 - specialised services for drug users (NSP, OST, consumption rooms, addiction treatment) — these can be with lower or higher threshold;
 - social services (accommodation, employment, social benefits);
 - HIV/HCV/HBV or other drug related infectious disease testing services;
 - general health services.
- Existence of a registry of clients (the list provides a sampling frame from which a random sample can be drawn; it does not have to be a name-based registry).
- Low- or high-threshold service (low-threshold services must implement some special provisions aimed at facilitating the access of current users to the provision of such services, e.g. a location near street drug markets, no appointments required, extended opening hours at night, etc.).

3. Treatment demand indicator ⁽¹¹⁾ — In many European countries an established system exists monitoring drug users in contact with treatment services (out- and inpatient), also collecting a limited set of behavioural indicators on a routine basis. Provides comprehensive national data.
 - Very low cost and appropriate where treatment services are widely provided and easy to access, but not recommended when a large proportion of the population is not in contact with addiction treatment services, and where provision of such services is limited.
 - As such systems rely on clinical reports, data are not directly provided by clients and so may be subject to biases ⁽³⁾.
 - The users in contact with addiction treatment may differ from those outside of treatment. In cases where coverage is low it can be advisable to concentrate on those entering treatment to be more representative of the population, but if the coverage is high it may be more practical to include all those currently in the treatment system, and supplement such sampling with other approaches.
4. Closed-settings patients — Drug users found in detoxification, rehabilitation centres. Usually high-threshold settings.
 - Easy access and logistics of the study, but, similarly to other treatment based surveys, there might be problems with the representativeness of the sample.
 - The behavioural indicators should be asked for the time period before admissions (e.g. last 4 weeks before entering treatment), although this might lead to stronger recall bias.
5. Prisons — The prison population constitutes a specific subset of closed settings. The prison population may also be a target population for studying risk behaviours and transmission in prison settings. As not all prisoners are drug users or IDUs it is important to present results separately for ever- and never-IDUs, potentially splitting the never-IDUs into (current) problematic drug users and others.
 - Drug users under arrest constitute a particularly vulnerable population.
 - In some countries prisons may in fact provide access to a quite large proportion of the drug using population depending on how frequently they are arrested.

Additionally, the sampling frame will usually have further restrictions, for example:

- Geographical area — For logistical reasons it may not be possible to run a countrywide survey. Some recommendations on selecting the geographic area are available in (2) and (4). The surveillance plan should take into account possible shifting of the geographical coverage in order to ensure timely detection of outbreaks, or combining areas with one-off assessments (e.g. in the case of outbreaks or indicators of increasing risk) with areas with on-going repeated data collection for long-term comparable monitoring over time.
- Adult population — Often surveys include only the persons legally able to give informed consent (e.g. over age 18); in some countries this might exclude young drug users at high risk, although in most European countries this is unlikely.

It should be noted that the representativeness of the sample might be further limited by non-response:

- Persons *not* consenting to participate.
- Persons *not* capable of participating in the survey and completing the questionnaire (e.g. excluding those intoxicated at the time of interview).

In some studies it has been possible for interviewers to keep track of non-responses by counting non-responders and noting a few characteristics (e.g. gender, estimated age group, observed ethnicity/language).

V. Sampling methods

In practical applications it is never possible to include all members of the target population in the study. Thus the outcomes of the study are estimates of the true values based on a sample of members of this population. These estimates can differ from the real values due to random variation or systematic bias in the recruitment and/or measurement.

Many of the sampling designs developed for epidemiological studies are not easy to implement in the studies concerning drug users, as there usually exists no list to sample from (they are a hard-to-reach, hidden population). The approaches adopted in surveillance and research studies among IDU often rely on convenience sampling although efforts are made to develop techniques allowing more rigorous measurements.

The disadvantages of convenience sampling must be noted:

- no statistical theory to provide an estimate of the indicator and the precision of the estimate;
- likely to suffer from selection biases, which are difficult to describe and quantify;
- less useful to monitor trends or compare across regions or countries as differences may be attributed to differential sampling.

Designing a sampling scheme:

1. Define the **TARGET POPULATION**, population of interest — the population that the results will be generalised to.
2. Establish a **SAMPLING FRAME** — the sub-population of the target population, from which the sample will be drawn; it has to be well defined and accessible for recruitment.
3. Take a **SAMPLE** from the sampling frame — if there exists a list of units in the sampling frame then randomly select a sample of units.

Overview of sampling methods for drug users

- Convenience sampling at services and venues (services aimed specifically at IDUs) — Needle and syringe programmes, substitution programmes, addiction treatment programmes other established health services; more open venues — homeless hostels, drop-in centres and social venues/settings).
It limits the sampling frame to populations that are easier to access, despite the possibility that these can be different in terms of behaviour and prevalence of infectious diseases from the subgroup not in contact with services. Clients are invited to the study as they attend a service/venue (convenience sample).
- Convenience outreach sampling — Effort is made to recruit the population possibly not in contact with services (community) through reaching them in open settings.
This may be the first step in cases of very stigmatised hidden populations in places where coverage of services is poor and target group members may be reluctant to provide information on their peers.
- Systematic or random sampling at services or from registries — Some services and treatment centres may maintain a registry of users, from which a random or systematic sample can be taken. Usually, multi-stage sampling would be implemented, by first sampling the services (clusters) and then sampling the target group members from each selected service unit. The target group members selected from the service unit registry may be contacted by the service or recruited at their next scheduled visit if applicable. (This may result in difficulties due to participants not showing up at scheduled visits.)
In this approach the sampling frame is narrowed to the population in the services, who can differ from the users outside the services. One example would be to implement a (sero-) behavioural survey as part of a treatment demand indicator (TDI) or to use random sampling from any other system registering drug users.
- Snowball sampling — This is a chain-referral method for efficient collection of convenience community sample. Each of the respondents is asked to provide contact details for other target group members, who can then be contacted by researcher.

As snowball sampling requires information to be provided on additional target group members it may not be practical in settings where the target group is highly stigmatised.

- Respondent-driven sampling (RDS) — RDS is a chain-referral method, in which each respondent is asked to recruit another from their social network by providing them with a study coupon, later shown to the research team to enter the study. The technique relies on a dual incentive system, providing an incentive for both participation in the study and for each successfully recruited member of target population.

RDS (like snowball sampling) takes advantage of social networks and will not work in instances when the population is poorly networked. In order to provide unbiased estimates through RDS the assumptions of the recruitment process must be met and appropriate statistical methods employed. There is no scientific consensus whether RDS works or not in practice to produce unbiased estimates (^{12, 13}). However, even if RDS may not provide unbiased estimates and the un-adjusted estimates may be used, it can be used as an efficient recruitment strategy for obtaining a convenience sample.

- Time-location sampling (TLS) — TLS assumes mapping of places of aggregation of the target population (public venues, open settings), assuming that different populations can frequent these at different times. A sampling frame of 'site-time interval' units is constructed, then such units are sampled and then target group members from each units (i.e. those attending at a specific time at a specific site).

TLS provides access to the target group as long as they congregate at venues that are accessible to researchers. Different patterns of attendance at those places can be corrected for at the stage of analysis.

Comparison of sampling schemes and recommendations

Currently, different guidelines recommend different approaches (summarised in Table 3). A specific study must take into account the characteristics of the local drug scene, coverage of services, the target group they wish to reach and the level of stigmatisation/marginalisation of the target population.

Table 3 — Approaches to sampling recommended by other guidelines.

Guideline	Survey type	Preferred sampling method	Alternative
(FHI, 2000) (3)	Behavioural survey	Time-location sampling (TLS)	Targeted, snowball recruitment at sites
(UNAIDS/WHO, 2011) (5)	Bio-behavioural	Respondent-driven sampling (RDS): starting seeds from community	TLS: at street venues where people inject Convenience: list of treatment centre attendees
(ECDC, 2010) (4)	Behavioural: population reachable in known settings and not severely stigmatised Behavioural: the population is not very well known, not easy to reach, and/or stigmatised	Service based or venue based, or on entry to addiction treatment depending on local service provision settings and coverage RDS if networked population TLS if not networked population Community outreach if not networked and mapping difficult	
(CDC/GAP, UCSF, 2010) (6)	Bio-behavioural: existing centre that serves IDUs in the area and routinely collects blood Bio-behavioural: limited services, IDUs congregate in accessible locations Bio-behavioural: limited services, no accessible congregation location or safety issues	Service based sampling using unlinked anonymous testing (UAT) TLS or targeted sampling RDS	

Selecting the right sampling approach may be of key importance for the use in surveillance. Surveillance requires a systematic, routine approach, for example repeated surveys, based on which major indicator trends should be detectable. On the other hand, surveillance often implies less rigorous approaches and less precise data than well-funded local research studies may obtain. The existing guidelines draw attention to the representativeness of the data, repeatability of the study, costs and simplicity. There is little evidence from the guidelines which of the criteria should be prioritised. Nonetheless, the efforts to achieve a more representative sample may compromise the simplicity, timeliness and sustainability of a system⁽¹⁴⁾.

In some sites in the United States and Europe (especially Western Europe) the majority of drug users remain in contact with services, and services may provide access to a sufficiently representative IDU group for the surveillance use. In the European setting, especially where service coverage is high, most surveillance systems will opt for service-based sampling as one of the central components of the system. This would ideally include low-threshold services where drug users can attend without appointment and outpatient treatment services but may also include closed services such as inpatient treatment services. In countries where drug users are often arrested prisons may be included as well. Depending on resource availability, studies should consider whether to add community sampling to the system to improve generalisability, for example through RDS (which can be initiated from drug users in contact with the services, and the interviews may even be held at service premises⁽¹⁵⁾), TLS or the other community sampling methods (e.g. venue based convenience sampling).

In countries with very low service coverage (e.g. <20–30%), service-based sampling may not be appropriate as the main surveillance tool and there is greater need for community sampling, still potentially starting from users in services and using existing facilities.

Surveillance criteria

1. Operational simplicity and reasonable cost (the system should be sustainable within public health structure).
2. Picking up new trends (reproducibility over time implies that detected changes reflect trends in population).
3. Validity of information (representativeness of the sample and valid measurement).

Table 4 — Advantages and disadvantages of different sampling schemes.

Sampling scheme	Circumstances when possible	Advantages	Disadvantages
Service, venue-based sampling	Existing services for IDUs such as NSP, OST and other venues well accessible for IDUs, high coverage.	Logistically simpler, lower cost, sustainable.	IDUs frequenting the services may differ from those not frequenting the services. If services and venues have poor coverage and are not well accepted the study may be inefficient.
Convenience community sampling	The population is very hidden and not networked, difficult to map congregation places.	Allows contact with the target population.	Non-probability design, possibly biased but bias cannot be estimated. Reluctance to participate.
Snowball sampling	The population is networked. Not very stigmatised.	Efficient. Potential to reach the hidden subpopulation.	Sampling bias resulting from initial seed selection, overrepresentation of more cooperative individuals and individual with larger contact networks (^{16, 17}).
Respondent-driven sampling	The population is networked. Best if average personal network contains >20 target group members. Well-networked and dedicated seeds can be identified.	Controlled conditions at study site. Efficient. Potential to reach the most hidden population. Offers a way to correct for network sampling biases.	Higher cost (incentives, costs of hiring the recruitment place). Bias resulting from not meeting the RDS assumptions. Dependant on willingness of the population to travel to the study site. Difficult to assess response bias (^{13, 12}). Disconnected subgroups may be missed. Large design effect (need to increase sample size) (¹⁸).
Time-location sampling	Relatively open drug scene so that the places where target population congregates can be identified.	A place to interview/take sample may not be available. If assumptions met — assumed to approach a probability sample.	Bias from non-inclusion of important sites, subpopulations not frequenting the type of sites at all, reluctance (disqualification due to intoxication) to participate at venues (¹⁹). For drug users often the sampling frame in reality is drug users in contact with services (²⁰). Difficulties in identification of target group members to be approached. Difficulties in interviewing/testing/collecting biological specimen in field conditions. Safety concerns. Weather factor. Reluctance to disclose sensitive information in public space. Drug users who do not congregate in public are usually missed.
Targeted sampling	Target population well know, described. Places of congregation can be	Responsive to new insights (e.g. inclusion of newly identified	Resources needed to conduct thorough ethnographical assessment makes it difficult to use for surveillance. Difficult to interview/test/collect biological specimen in field conditions. Safety

identified.	subgroups). Abundance of qualitative information for interpretation.	concerns. Weather factor. Reluctance to disclose sensitive information in public space. Low proportion of eligible subjects among initially screened potential respondents ⁽²¹⁾ . No formal way to assess representativeness, potential bias due to fluctuation of population during different hours at the same site. Drug users who do not congregate in public are usually missed.
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VI. Formative research

Formative research is usually necessary for all study designs. It informs sampling design (choice of the type, specific procedures) as well as the content of the questionnaire and later interpretation of data. Depending on the purpose of formative research (i.e. what information is sought), quantitative and qualitative methods may be used. The information that needs to be collected at this stage varies according to the selected study design (Table 5).

'Formative assessment is the process by which researchers or public health practitioners define the community of interest, ways of accessing the community and the attributes of the community relevant to the specific public health issue.'⁽⁵⁴⁾

1. Revision of existing data

Formative research may often start with revision of existing data, including a literature search and review. Existing data may provide information on geographical variations in injecting drug use, indicate the groups that may be especially at risk of infections (age groups, gender, place of residence). If prior research has been done, some indication can be found on the potential non-networked subgroups in the population or the specific risks undertaken by the population, and patterns of drug use. It may also be possible to discover if the target population is reached by services that are currently in place.

The following data sources might be of use: data on people living with HIV whose transmission mode was IDU; data on diagnoses of HCV and HBV where the transmission mode was IDU; police data; emergency room admissions data; dependence treatment admissions data; other medical care data (including testing sites data); programme provision/evaluation data; other published and unpublished research; death registries.

In the case of consultations with key informants (expert interviews), sometimes the data would not be collected, or not all of it would be included in a database (e.g. police operational notes, programme provision notes), so the staff may be consulted regarding specific questions.

2. Qualitative methods

Qualitative research is especially useful in order to obtain culturally specific information about the values, opinions, behaviours, and social contexts of particular populations⁽²²⁾.

- a. **Ethnographic research and participant observation:** In this method the researcher observes and to a varied extent participates in the activities of the target population in the places where the activities normally take place (community settings). During the observations researchers interact with the members of the population and record their observations. Ethnographic observations should be conducted in a systematic way. Locations should be visited at different times of the day and on different days of the week. The researchers should have a list of questions they wish to ask in order to generate information during the sessions. IDU indicators should be collected, for example the presence of used syringes, baggies, balloons or injection works/equipment, as well as behavioural indicators such as coping activity, loitering or commercial sex work. Ethnographic/participant research can be very time consuming, and can often take several months to complete.
- b. **In-depth interviews with key informants who have knowledge of the local IDU community:** The key informants may include, for example, local HIV prevention personnel, community planning group members, law enforcement representatives and current or former injectors. The in-depth interviews are conducted by asking neutral questions to elicit free response from the participant, following up on the response in a non-leading, non-judgmental way. They are usually conducted face-to-face, typed and the transcripts are analysed. The aim is to obtain personal perspectives (feelings, opinions, experiences) on the research subject, especially on sensitive topics.
- c. **Focus groups with active or former drug users:** Focus groups are designed so that researchers can learn the group norms and attitudes for group norms and whether there is any variety of opinions in the target population. One researcher acts as moderator, asking

open-ended questions to the group (8–10 people from target population) while the second researcher takes a record of what is said.

For more practical information on the qualitative research considerations please see (22) and (23).

Table 5 — Information to be obtained by up-front formative research, by the recruitment methods planned for the main study.

Recruitment method	Information necessary	Source/method
Service-based sampling	List of services and operational hours; existence of registries; number of clients; logistics for interviewing/collection of samples.	Revision of existing data (programme data, police data); consultation with key informants.
Time-location sampling	List of venues frequented by the target population.	Revision of existing data (programme data, police data); consultation with key informants.
	Times when target group members attend the venue. Characteristics (e.g. age, drug use patterns) and number of target group members at the venue at different times. Safety issues and logistics for interviewing/collection of samples.	Participant observation.
Respondent-driven sampling	Characteristics of social network formed by IDU (number or ties, existence of disjoint subgroups). Acceptability of the RDS procedures. Selection of seeds. Survey logistics (hours, site), incentive, design of coupons ⁽²⁴⁾ .	Expert interviews. In-depths interviews.

VII. Study site requirements

The sites where the study can be conducted will differ according to the design of the study. In cases where surveys are carried out among clients of services or patients of treatment centres — and also possibly for RDS — there will be established study sites. However, in TLS and targeted sampling the contact with respondents often takes place at the venues where the target population congregates. This has important implications, for example for the acceptable length of the questionnaire, biological samples collection or the willingness of target group members to take part in the study.

1. Location of the site:

Due to legal issues and/or social stigma it is often undesirable for the drug users to be identified as drug users. The study site should therefore be discrete and, if feasible, not identified by the local community as a site for drug users (e.g. avoid large signs).

The location of the study site should not interfere with local community habits, (e.g. avoid creating increased activity at late hours, which may cause disturbance in residential districts).

The site should be accessible, i.e. easy to find and reach by public transport. A long distance between the site and areas where drug users live/congregate has been shown to be a significant barrier to participation in the study.

Study sites should not be located near law enforcement agencies, as this could discourage users from attending.

The safety of the site and the area where it is located should be also considered. Safety issues may become problematic especially for TLS or targeted sampling.

2. Rooms/space at the site

The study site should have a waiting area, interview room(s) or other private, quiet space to conduct interviews, a biological sample collection area and a bathroom. Participation in the study should be pleasant — participants should be welcomed as they enter, and, if affordable, refreshments should be available in the waiting area.

Requirements regarding the place where biological samples can be collected are often formalised in local regulations. Collection of blood through venepuncture may be associated with the most restrictive requirements. Additionally, collection of some specimens may require hiring a health care worker. Some types of biological samples cannot be stored at room temperature before transporting to the laboratory.

Some space has to be dedicated to storage of study materials. If this includes biological samples the site should have a refrigerator or freezer. The completed interviews should be stored in a place with restricted access (e.g. a locked cupboard).

When using TLS recruitment, the possibility of hiring an ambulance/van should be considered. Since the interviewing space is usually organised in a public place (e.g. bar/restaurant, car), the conditions may be suboptimal (not sufficient light, noise), which means the questionnaire should be short and printed in sufficiently large font.

3. Informing police, city authorities and other institutions

Police, law enforcement agencies, local authorities and neighbouring businesses should be informed of the study and location of the study sites, and if possible be invited to be co-responsible (e.g. as part of an advisory board or by regularly informing them on progress, perhaps through emails). This will prevent the investigation by law enforcement of the unusual activities connected with the study and allow them to manage potential complaints from the community.

4. Staff safety

Security procedures must be in place at the study site. Implement procedures to prevent large numbers of clients from congregating at the study site. People who are very intoxicated or who behave in a threatening way should not be allowed into study site.

The procedures for exposure to potentially infected blood should be clarified together with the responsibilities (including financial obligations, insurance) of the study coordinator in case there is a need for post-exposure prophylaxis.

5. Using existing premises

Sites that are established in existing services, especially those targeted at drug users, offer the advantage of staff trained in contacting the target population, existing safety procedures, existing facilities to collect biological material and private space for interviews.

The disadvantage may be that the place is associated with drug users and serves a specific subgroup of users (e.g. the most marginalised group), which would discourage other subgroups from participating.

Study site selection considerations are provided in (25).

VIII. Principles of laboratory diagnoses for HIV and viral hepatitis

Standard diagnostic tests and procedures will in most cases also be relevant for surveillance use. The procedures typically rely on screening assays later confirmed with another (more specific and usually more costly) test. The full diagnostic process may not be necessary from the epidemiological point of view, especially if the prevalence is high. Similarly, the less precise tests may be selected for reasons of simplicity of use and costs (e.g. biological specimen other than blood). Some of these tools are available solely for research purposes, but not licensed as diagnostic tools. However, for bio-surveys the recent tendency is to consider it ethically important to always provide individuals with a test result, and therefore diagnostic and confirmation tests should be considered.

HIV infection

Step 1. Screening (first line) assay

Current screening assays rely on the detection of antibodies to HIV or the antibodies and antigen p24 (IVth generation tests). At present, the IVth generation assays are commonly used due to a shorter window period (i.e. the time after infection when the test is still negative) ⁽²⁶⁾. Depending on the settings, conventional or rapid (Point Of Care) tests may be used. The biological sample required is typically blood (venous or capillary), oral fluid or urine. Currently used laboratory screening assay have sensitivities between 99.8 % and 100 % and specificities up to 99.8 % ⁽²⁷⁾.

Step 2. Confirmatory (supplementary) assay

The confirmation assays may be based on confirming the presence of antibodies (Western Blot, WB; line immunoassay, LIA; indirect immunofluorescence assay, IFA) or detection of viral genetic material (nucleic acid amplification methods, NAAT, most commonly polymerase chain reaction, PCR). These tests are always laboratory based.

The actual diagnostic algorithm in place (using particular tests, especially rapid tests, repeating tests, two samples requirement) may vary and countries may adopt a certain algorithm; the work on an updated unified algorithm is ongoing ⁽²⁸⁾. Apart from laboratory procedures, it is considered good practice to perform pre- and post-test counselling. Such counselling covers individual risk assessment, benefits of testing, follow-up issues such as partner notification and linkage to care ^(26, 29).

Interpretation of results

1. The window period for tests based on antibody detection is on average 2–3 weeks (almost everybody seroconverts by 12 weeks), the time it takes for the body to produce detectable level of antibodies after infection. The tests, which detect p24 viral antigen, have a window period of only several days to 2 weeks and the tests detecting the presence of viral genetic material 3–5 days less. In cases of early infection detected with IVth generation assay, confirmation assays based on antibody detection are of less use. In these cases NAAT methods or p24 neutralisation assays are used for confirmation ⁽²⁶⁾.
2. Both confirmation of antibodies and genetic material provide evidence of active HIV infection in adults.
3. Attention should be paid to the choice of assays in cases where there is a significant proportion of HIV-2 or HIV-1 subtype O, as some tests may be suboptimal/not able to detect such infection. These viruses are more common among migrants from Africa.
4. If the prevalence in the target population is high (>10 %) the positive predictive value (per cent of positives confirmed by confirmatory assay) of screening assays is high and the screening results are sufficient for epidemiological purposes. However, in cases where there is low prevalence it is recommended that only the confirmed results are reported.

Additional tests of epidemiological importance

Further tests of epidemiological importance may include subtyping, testing for resistance to monitor the level of transmitted resistance in treatment of naïve patients and recent infection testing algorithms (RITA), which allow positive samples to be classified as coming from patients with recent (approximately <6 months) or long-standing infection⁽³⁰⁾. RITA tests are currently mainly used for surveillance purposes (i.e. the results are not communicated to the patients) and enable HIV incidence to be estimated⁽³¹⁾.

HCV infection

Testing algorithm

HCV testing is also a process based on a series of screening and confirmatory assays from blood samples. The first step assays now most commonly in use are the third generation enzyme immunoassays with improved accuracy (specificity >99 %) and a window period of 1–10 weeks from exposure. Screening assays are usually laboratory based, although there exists one rapid test approved for diagnostic purposes in the EU (CE-marked), that can be also done from oral fluid⁽³²⁾.

The gold standard to confirm active infection is the nucleic acid test for detection of HCV RNA (pcr). Recently, a new test detecting HCV core antigen was developed that can also confirm active infection⁽³³⁾. Presence of HCV specific antibodies can be confirmed by recombinant immunoblot assays or Western blot test.

Interpretation of results

1. Recognition of HCV infection has to take into account that, unlike HIV, the HCV virus can be eliminated either naturally or in consequence of treatment. Antibodies to the virus, which are detected by the first step (screening) assays, usually persist even in cases of resolved infection⁽³⁴⁾.
2. In some cases, infection may persist in the liver even though both antibodies and serum HCV RNA tests are negative (occult infection)⁽³⁵⁾.
3. Screening tests may have lower sensitivity in haemodialysis and immunocompromised patients.
4. In low prevalence settings (<10 %) in testing for epidemiological purposes the screening assays would require a confirmatory test. However, it is now recognised that in cases of a high signal in the screening assay the positive result is confirmed in >95 % of cases⁽³⁶⁾.

Additional tests of epidemiological importance

At present, diagnosing acute infection if seroconversion is not documented by a negative result followed by a positive one remains a challenge.

Further tests of epidemiological importance may include determination of genotype, which is important for treatment outcomes. Genotype analyses sometimes allow the origins of the virus in an epidemic to be pinpointed, although this may be of limited use for prevention purposes. A virus of a specific (e.g. non-national) origin may circulate among both nationals and non-nationals independently of its original introduction.

HBV infection

HBV infection in adults is most commonly an acute illness, which resolves spontaneously. However, markers of past infection can be found in the blood. In 5–15 % of cases the virus is not eliminated from the body, leading to chronic hepatitis B, which can be diagnosed based on blood tests. In significant proportion of cases with apparent resolved infection the virus continues to replicate in the liver (occult HBV infection).

Laboratory diagnosis of HBV and its clinical stages is complex. For surveillance studies usually the following laboratory parameters are used: HBsAg, anti-HBs, anti-HBc, anti-HBc IgM. Table 6 shows the interpretation of laboratory results.

Table 6 — Interpretation of laboratory results of HBV infection ⁽³⁷⁾

HBsAg	Anti-HBs	Anti-HBc (total)	Anti-HBc IgM	Interpretation
-	-	-	-	Susceptible
+	-	+	-	Active infection
+	-	+	+	Active infection, most likely acute
-	+	-	-	Uninfected, immune due to vaccination
-	+	+	-	Most likely resolved infection (immune)
-	-	+	-	Unclear: resolved infection (most common); false-positive anti-HBc, thus susceptible; low level chronic infection; resolving acute infection

Further tests may include genotype testing. There are other serological markers of HBV infection of value in the clinical management, such as HBe-Ag or HBV-DNA that remain outside the scope of this document.

Tests available from different biological samples are summarised in Table 7. For more details on how to select a test and collect biological samples refer to Annex 2.

Table 7 — Tests available from different biological materials.

Biological material	HIV tests available	HCV tests available	HBV tests available
Whole blood	Rapid HIV tests (antibody tests and antibody/antigen p24 test)	Rapid anti-HCV test	Rapid HBs antigen test, antibody tests less sensitive ⁽³⁸⁾
Serum/plasma	Rapid HIV test Laboratory based screening assays (antibody and antibody/antigen p24) Laboratory based confirmation serologic assays Molecular tests	Rapid anti-HCV test Laboratory based assays Laboratory based confirmation serologic assays Molecular tests	Laboratory based assays — antibody tests and HBs antigen Molecular tests
Dried blood spots (capillary blood)	Laboratory based screening assays (antibody and antibody/antigen p24) Laboratory based confirmation serologic assays Molecular tests	Laboratory based assays Laboratory based confirmation serologic assays Molecular tests	Laboratory based assays — antibody tests and HBs antigen Molecular tests
Oral fluid	Rapid HIV antibody test, laboratory based screening	Rapid HCV antibody tests Laboratory HCV test (also	HBs antigen test (also with saliva)

	assays Laboratory-based WB	with saliva)	Antibody tests are not sensitive enough
Urine	Rapid strip HIV antibody test (rarely used)	Not available	Not available

X. Questionnaire design and administration

The questionnaire is the main measurement tool in behavioural studies. Questionnaire and questions should be designed to reduce bias due to non-response, question refusal, misinterpretation of questions or differential administration of questionnaire by the interviewers. Therefore the researchers may often decide to go through a lengthy process of validation and testing of a questionnaire and interviewer training before a survey is implemented. Generally, a questionnaire should be at least informally reviewed by some target group members.

An example questionnaire can be found in the *DRID Guidance Module: Behavioural indicators for people who inject drugs*, which includes questions that enable internationally adopted indicators for IDU to be constructed.

Questionnaires in surveillance

1. Harmonisation with other monitoring systems as well as with the previous rounds of the survey should be assured.
2. The use of already developed standardised questions shortens the testing phase.
3. Accuracy of translation and cultural context must be kept in mind when using questions developed internationally.
4. Questions adopted for DRID monitoring are available in *DRID Guidance Module: Example Questionnaire*.

More information on questionnaire development can be found, for example, in (39) and (40).

- General rules for designing a questionnaire:
 - All information necessary to fulfil the study objectives should be collected, but unnecessary questions should be avoided (i.e. the use of each question in the final report should be clear).
 - Questionnaires that are very long may result in a lower response rate and lower quality of data, especially if data are collected in field conditions.
 - The questions used should be validated and pre-tested.
 - Each question should be designed to obtain one piece of information. Questions should be unambiguous (who, what, when, where). Open-ended questions should be avoided.
 - The questionnaire should start with a sentence explaining the purpose of the study and data use.
 - The section dealing with the key issues (e.g. exposures of main interest) should be asked first and classifying information (e.g. demographics) should be moved towards the end of the questionnaire. The most sensitive questions should not appear at the beginning.
- Types of questionnaire:
 - Self-administered questionnaire or questionnaires administered by interviewers:
 - Self-administered questionnaires should be simple and short. They may be more useful when asking sensitive questions.
 - Interviewer-administered surveys allow for questions to be clarified, additional techniques can be applied (showing additional materials, probing, aided recall), the questions can be arranged in (alternative) sequences asked only when applicable. There is also a better control over completeness of responses.

- Form of the questionnaire:
 - Paper or electronic format questionnaires may be used. Electronic questionnaires offer the advantage of automatically displaying the inconsistent or not completed responses and reduce data-entry errors.
 - Depending on the device and if the data are entered by the interviewer (personal interviewing or telephone interviewing) or by the respondent the following abbreviations for electronic formats are in use: CAPI: computer assisted personal interviewing; WAPI: web assisted personal interviewing; CASI: computer assisted self-interviewing; CAWI: computer assisted web interviewing; CATI: computer assisted telephone interviewing; TAPI: tablet assisted personal interviewing; TASI: tablet assisted self-interviewing; SAPI: smartphone assisted personal interviewing; SASI: smartphone assisted self-interviewing.

- Testing questions and questionnaires:

Each question should be tested. However, additionally there might be some contextual effects depending on where the question is placed in the questionnaire.

The testing phase can include the following:

- Expert review is often the first step in questionnaire testing and involves experts working in the field experienced in conducting similar surveys.
- Interviewer and target group focus groups
 - The questionnaire is administered first to interviewers and then to a small sample of target group members.
 - The following issues should then be discussed during focus groups: general impression of the question, clarity of wording, interpretation of the question by respondents, appropriateness of response categories, ordering of the questions in the questionnaire (different orderings can be used and responses compared).
- A cognitive interview is conducted with a limited number of target group members
 - Cognitive phases of reaching the answers are solicited through thinking out-loud, paraphrasing the question, listing information used to reach the answer.
 - Cognitive interviews allow researchers to study the understanding of the questions, interpretation of the terms used, of response categories, the feasibility of recall and if questions are sensitive. Alternative wordings can be tested.
- The piloting phase is the last phase of questionnaire development (after corrections from the pre-testing phase) and should be conducted under similar conditions to which the survey will be implemented in practice.
 - Verifying assumptions used in sample size calculation (frequency of exposures, response rate), acceptability of the study, rate of question refusals.
- Interviewer training aims to minimise differences between interviewers in the way the survey is conducted that can potentially introduce measurement bias.
 - It should include the overview of the study, including objectives and procedures (recruitment, questionnaire, biological sample collection, collecting results), review of all the questions, safety procedures and procedures for unexpected situations, monitoring, logistics and administrative issues. Importantly, interviewers should feel

comfortable about all the questions (e.g. understand all the terms used, understand where special techniques are required, such as probing or memory enhancement techniques).

- Interviewers should be trained to deal with foreseeable reactions of the respondents, such as a critical or overly enthusiastic attitude to the whole study, interrupting, question refusals, expressing doubts, responses not included in the list.
- Interviewers should recognise not to express personal feelings and opinions and to phrase the questions exactly as formulated in the questionnaire.

XI. Ethical considerations

Research concerning human subjects (including studies concerning human health-related behaviour in a variety of circumstances and environments ⁽⁴¹⁾) should be based on the main principles outlined in the Belmont Report ⁽⁴²⁾, Declaration of Helsinki ⁽⁴³⁾ and CIOMS/WHO International Ethical Guidelines for Epidemiological Studies ⁽⁴⁴⁾ (see box). Some issues specific to drug use research are presented in ⁽⁴⁵⁾.

All bio-behavioural studies must undergo review by medical ethics committees. Specific requirements may depend on local regulations. Some common problems pertinent to studies among drug users are outlined below.

Informed consent — A process that involves three elements: information, comprehension and voluntariness.

- Information for the potential participant: This covers the research procedure, research purpose, risks and anticipated benefits, potential secondary use of data and specimen, person responsible for the research and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research ^(43, 41, 44, 51).
- Coercion: This may occur if there is a dependency relationship between the potential participant and the recruiter, or if incentives are excessively high. Appropriate incentives are acceptable ⁽⁴⁶⁾.
- Oral or written consent: As a rule, informed consent should be documented by a signed form. An ethical committee may approve oral consent in cases of research carrying no more than minimal risk to the subjects. The requirement for signed consent may be waived in cases where the existence of signed forms may threaten subjects' confidentiality. In such cases it might be considered appropriate for the interviewer sign on the questionnaire that the informed consent procedure has been followed.

Ethical principles:

Respect for persons — autonomous decisions and protection of those with diminished autonomy.

Beneficence — avoiding harms; minimising risks and maximising benefits.

Justice — those who bear the burden of research should be the ones who will benefit from its results.

Vulnerable population

- Drug users as a population with diminished autonomy (i.e. with diminished capacity to take independent decisions due to, for example, economic or legal drug-use related factors): Special attention needs to be paid to voluntary participation in research, especially in settings like prisons. For some research additional procedural protective measures may be required ⁽⁴¹⁾.
- Protecting privacy and confidentiality of the subjects at the time of interview, testing and data processing: The potential harms caused by a bio-behavioural study include psychological distress, legal problems or economic loss. Harms and benefits at the level of the individual participant are given special weight. However, risks to communities should be also considered, such as stigmatisation of the group due to risk behaviours or high prevalence of infectious diseases.

Benefits to the community

- The participants should be provided with benefits such as test results, information on infectious diseases and counselling, and referral to appropriate services.
- The current guideline is that the participants have the right to be informed about the general findings of the study and any information that relates directly to their health (i.e. the results of tests) ⁽⁴⁴⁾.

Specific considerations in chain-referral studies⁽⁴⁷⁾

- Snowball recruitment may require disclosure of information about a third party without their consent, which raises concerns. A solution could be providing the respondent with an information sheet and let the respondent contact potential nominees.
- Discovering serologically discordant partnerships.
- (Especially in RDS) coercion by peer recruiter. A solution is modest remuneration, limited number of coupons, obtaining informed consent by the staff at the start of the interview.

XII. Aspects of statistical analysis

Database and data management

When carrying out repeated surveys, especially when run through services, a professional database should be considered to allow more efficient data storage and management and possibly data entry/uploading through dedicated web tools. The design of the database and data entry process can have an impact on the overall quality of the data. Resources allowing, it is recommended that data is double entered.

For one-off studies there exists readily available software, such as Access or Epi Info (www.cdc.gov/epiinfo/), allowing ad-hoc simple databases to be designed, with an electronic entry form. The process is described in, for example, (5) and (48).

Hints for creating a database and entering data:

- A code book with a description of each field (variable) and coding should be created.
- Each field should contain a single piece of information (an answer to a single question or well-defined indicator).
- Responses should be coded (according to a list to select from, provided on the form), question refusal and missing data should have different codes, additional fields for comments should be available (see also DRID Module Example Questionnaire).
- Build in checks for consistency (implausible values, e.g. extreme age values, dates sequences, contradictory answers).
- Include required fields, especially for 'administrative' variables (e.g. date of interview).
- Train data entry staff.

Overview of analysis process

Epidemiological measures

In surveillance studies we focus on occurrence and associated factors of diseases (infections). The basic epidemiological measures, which we usually aim to estimate from studies, include:

1. Measures of frequency of disease, infection or another characteristic of interest — prevalence, odds and incidence
 - The incidence of infection gives information about the current risk of contracting the disease. Typically it is estimated from cohort studies of negative users. These studies are often logistically difficult to establish and are time and resource consuming. Statistical and mathematical modelling can help estimating incidence from other types of data.
 - Prevalence is an outcome of both the risk of infection and duration of disease. High prevalence may persist for many years after an outbreak.
2. Measures of association (of disease with an exposure) — relative risk (RR) or risk ratio, prevalence ratio (PR) and odds ratio (OR).
 - The best measure of association (of the effect of exposure on the outcome) is relative risk. However, it is typically calculated only from cohort studies.
 - The prevalence ratio is calculated from cross-sectional studies and the odds ratio can be calculated from case-control studies as well as from cohort and cross-sectional studies.
 - The odds ratio approximates the RR if the prevalence is low (<10%).

Epidemiological measures:

$$\text{Prevalence: } P = \frac{\text{number of existing cases of disease at a given time}}{\text{population at a given time}}$$

$$\text{Incidence: } I = \frac{\text{number of new cases of disease during observation time}}{\text{population at risk of disease at the beginning of observation time}}$$

$$\text{Odds: } O = \frac{\text{probability of being a case in a population}}{\text{probability of not being a case in a population}} = \frac{\text{number of cases}}{\text{number of non-cases}}$$

$$\text{Relative risk: } RR = \frac{I \text{ among exposed}}{I \text{ among not exposed}}$$

$$\text{Prevalence ratio: } PR = \frac{P \text{ among exposed}}{P \text{ among not exposed}}$$

$$\text{Odds ratio: } OR = \frac{\text{odds of disease among exposed}}{\text{odds of disease among not exposed}} = \frac{\text{odds of exposure among cases}}{\text{odds of exposure among non-cases}}$$

Analysis process

1. Descriptive analysis: This includes summarising distributions (frequencies and percentages) of responses or laboratory results for categorical variables and typically calculating mean and median values with standard errors and interquartile ranges for numerical variables.
 - Measures of frequency of outcome are estimated (e.g. prevalence of infection) as the sample proportion for simple random samples or using an estimate appropriate for the sampling design.
 - Calculation of internationally agreed indicators is recommended (including the EMCDDA behavioural indicators in the *DRID Guidance Module: Behavioural indicators for people who inject drugs*).
 - The indicators could then be disaggregated (calculated separately) by gender, age group, region (and other potentially important groupings such as by drug of choice, injecting drugs status, etc.).
2. Univariable analysis (US sources often use the term 'bivariate'): During this step we examine whether there is an association between two given variables (usually outcome and exposure).
 - If one of the variables is categorical (i.e. defining groups described by each category) then these groups are compared in terms of means of numerical variable (parametric and non-parametric tests) or distribution of another categorical variable (testing for independence of the variables). In cases where there are two numerical variables a measure of correlation can be calculated.
 - This analysis can be performed in groups (strata) defined by a third variable. Tests are available to see if the association differs by strata.
 - For binary outcome variables the effect size of the association can be estimated (estimating RR, PR, OR).
3. Multivariable analysis: In multivariable analysis we are able to study independent effects of several explanatory variables (independent variables, predictors) on the dependent variable (response, e.g. presence of infection).
 - An association observed in a multivariable model is adjusted for possible confounding effects of other factors in the model.
 - Adding interactions between variables allows for a differential effect of a studied predictor by a third variable (effect modification).

For guidelines in basic statistical methods, including the flow chart of tests to use, see, for example, (49) (50) or (3).

Interpretation of results

1. Role of chance: Observed differences can be due to chance and the statistical tests aim to identify whether the difference is likely to be real ('statistically significant' results) or not. For small p-values (conventionally <0.05) we conclude that data do not support the hypothesis that there is no difference and we accept the alternative that there is a difference. There are two types of error with respect to true population values when performing a statistical test: either there is no real difference but the result is 'significant' (referred to as type I (α) error), or there is a real difference but the result is 'insignificant' (type II (β) error). The probability of the first error is determined by the researcher, by selecting the cut-off p-value, whereas the probability of the later depends, among other things, on the sample size and is useful in sample size estimation.
2. Confounding and bias: The association may be distorted by various systematic errors of sample selection (selection bias) or measurement of exposure or disease (information bias). Confounding can result if there exists a factor that is associated with exposure that also has an impact on the risk of disease. For example, a higher prevalence of infectious diseases among a population in treatment could be explained by a longer injecting career in the population. Confounding and bias are discussed in, for example, (3).
3. Causality: Even a valid statistical association does not imply causal association of an exposure with the outcome. Additional criteria have been developed to make the causality claim (⁵¹).

Survey data analysis

The sampling design has implications on the choice of statistical techniques. The majority of the techniques have been developed for simple random samples and when used for more complicated designs may give biased results (⁵²).

Analysis of TLS data

Methods for random samples are not appropriate for TLS data due to the following features of the design:

- Cluster effect (time-location clusters are sampled) — generally this design increases uncertainty.
- Heterogeneous probability of being sampled (due to different frequency of attending sampled venues) can affect both the estimate and the standard error.

Therefore weighting should be considered, such as in (53), in addition to accounting for clustering. The weighting also depends on the actual number of the persons enumerated during the sampling events and the number of interviews completed (⁵⁴).

Analysis of RDS data

RDS data require specific analysis methods that account for the sampling process through social links using a Markov chain model of the recruitment process.

- Necessary personal network size information: the number of friends from the target group that the participant is likely to meet during the time given for recruitment (typically the

The RDS assumptions:

The network is connected (i.e. there is a 'chain' of social ties to reach any member of the population, within the number of waves feasible during the study).

People can accurately report their drug using network size.

The sample size is small compared to the size of the target population.

Recruiters recruit from their personal network at random (and the non-response is not differential).

The recruitment is non-differential (equally efficient across different groups).

number of such friends that the participant in fact met during the past one to several months is asked for).

- The software specific to RDS data is RDSAT, available at www.respondentdrivensampling.org.
- If the theoretical assumptions are met (see box), the recruitment process reaches equilibrium (in practice, the majority of the sample should be recruited in long chains) and the homophily is equal across groups, the RDS estimators are unbiased (⁵⁵).

Apart from difficulties meeting the theoretical assumptions of the recruitment model, there are several shortcomings of the analytical tools available at present, such as no well-developed convergence diagnostics, limitation of the proper RDS inference to estimating population means, and no techniques to correct for non-response bias (^{56, 12, 13}).

Network data analysis is described in (57).

HIV incidence estimation from incidence testing in biological prevalence studies

For HIV seroprevalence studies there is also the possibility to estimate incidence. The estimation relies on an additional testing algorithm (RITA, recent infection testing algorithm), which allows infections to be differentiated as recent (with a test-specific window period, typically approximately 6 months) or longstanding. Formulas and further guidelines, including guidelines on sample size estimation and false recent rate adjustment, are available from the WHO HIV incidence website (⁵⁸). Prevalence among new injectors (<2 years from first injection) may also provide an estimate of ongoing transmission, although the incidence shortly after initiation of injecting may be higher than at the later stages.

Sample size calculation

The sample size should be determined based on the main characteristics to be measured (e.g. prevalence of DRID diseases) and the acceptable standard errors.

Often there is not sufficient evidence to assume one plausible value of prevalence and several reasonable values should be tried to gain insight into how large the sample should be in different scenarios.

The sample size estimates will be different in case of more complex sampling designs, including cluster and stratified samples as well as the ones used in chain referral and TLS techniques. In those cases the formula for the sample size contains an additional term — the design effect (DE) (⁵²) (see box below).

Depending on the particular design, there are formulas to calculate the design effect (DE). However, it is often only possible to calculate it in the post hoc analysis of the complex sample. Some guideline is available through past experience.

Wejnert et al. recommend that the DE for RDS studies should be at least 4 (updated from DE=2 recommended previously) (^{18, 59}).

Formulas for sample size (N) calculation:

$$\text{Random sample: } N = \frac{P(1-P)}{(SE(P))^2}$$

$$\text{Complex sampling design: } N = DE \frac{P(1-P)}{(SE(P))^2}$$

Where:

- P is the assumed proportion of population displaying a certain characteristic (e.g. expected based on prior evidence of prevalence of disease).
- SE(P) is the acceptable standard error.
- DE is the design effect.

XIII. Bio-behavioural studies as a surveillance tool

Bio-behavioural studies used in surveillance should be planned in a way that meets the basic assumptions of a surveillance system. This is defined usually as 'the on-going, systematic collection, analysis, interpretation, and dissemination of data regarding a health-related event for use in public health action to reduce morbidity and mortality and to improve health. Data disseminated by a public health surveillance system can be used for immediate public health action, programme planning and evaluation, and formulating research hypotheses' ⁽⁶⁰⁾.

When bio-prevalence studies are used for surveillance they should provide valid information (be representative) but also be repeatable over time (i.e. the same target population should be reached and measurements should be reliable), to assess trend over time ⁽⁵⁾.

Adapting to local context

In order for the surveillance efforts to be sustainable it is advisable to establish the system within the administrative framework of the country responding to local needs, addressing information gaps and using existing infrastructure.

The possible links and triangulation of data with other, existing or planned systems should be also discussed in order to maximise the use of the data ⁽⁶¹⁾. In European countries there exist case-based surveillance systems for infectious diseases including HIV, HCV and HBV infections. Other systems may be based on cohort studies of clients of services targeted at drug users, testing services, treatment demand monitoring systems. Guidelines on how to use data in the framework of second generation surveillance are available from UNAIDS/WHO and ECDC.

Repeated studies, geographical coverage

In order for the method to be a good surveillance tool it should provide consistent estimates over time; i.e., changes in estimates should reflect real changes in the epidemiology of infectious diseases and risk behaviours among the population of interest. This issue has not been well recognised but there are data to suggest, for example, high variability in repeated RDS studies ⁽⁶²⁾ and differential results depending on study settings in service bases studies ⁽⁶³⁾.

The frequency of the bio-behavioural surveys will have to be adapted to the local situation; for example, in cases of increased transmission an additional study may be planned. It should be noted that small changes in behaviour and/or prevalence may be difficult to detect (i.e. require large sample sizes) and may not be so important from the public health point of view. Despite smaller sample sizes, changes in prevalence may be detected more easily in some subgroups, for example among new injectors, a proxy indicator for incidence ⁽⁶⁴⁾.

IDUs tend to form local networks, which may have different norms for risk behaviours and different levels of drug related infectious diseases. The differences in prevalence between sites are often quite marked. Therefore multiple locations have to be sampled. The surveillance plan should include locations where there is evidence of injecting drug use (large networks) even if there might still not be any evidence of increased infectious disease transmission, although certainly the areas with highest transmission need to be included ⁽⁶⁵⁾. If there is a limited budget more frequent studies could be carried out in areas with higher risk and less frequent ones in areas at lower risk.

The agreed assessment indicators of implementation of DRID at the country level set out the minimum requirement of collecting biological markers prevalence data at least once per 3 years. This should be a reasonable target in cases of multisite studies. If studies involve changing geographic areas it might be acceptable to include each area at least every 4–5 years.

'It is important to remember that surveillance data will not be used if:

- the study is too time consuming (e.g. sample size too large);
- the study is too costly to repeat;
- the analysis is too complicated for local health departments to routinely do;
- the analysis is too complicated to understand for those who need the data.' ⁽⁵⁴⁾

Comparability between countries

Comparability of data between countries is one of the reasons to attempt harmonisation of surveillance methods across the countries. In terms of repeated surveys this process is particularly difficult and will depend on health care organisation, coverage of services, legal framework, available resources, etc. As a first step it is proposed that the same behavioural indicators (e.g. harmonising the recall period, see *DRID Guidance Module: Behavioural indicators for people who inject drugs*) and serologic markers should be used.

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Abbreviations

AIDS	acquired immune deficiency syndrome
CAPI	computer assisted personal interviewing
CASI	computer assisted self-interviewing
CATI	computer assisted telephone interviewing
CAWI	computer assisted web interviewing
CDC	Centers for Disease Control and Prevention
CIBERESP	Consortium for Biomedical Research in Epidemiology and Public Health, Spain
CIOMS	Council for International Organizations of Medical Sciences
DBS	dried blood spots
DE	design effect
DRID	drug-related infectious diseases
ECDC	European Centre for Disease Prevention and Control
EIA	enzyme immunoassay
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
FHI	Family Health International
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IDUs	injecting drug users
IFA	indirect immunofluorescence assay
LIA	line immunoassay
MSM	men who have sex with men
NAAT	nucleic acid amplification methods
NIDU	non-injecting drug users
NSP	needle and syringe programmes
OR	odds ratio
OST	opioid substitution treatment

PCR	most commonly polymerase chain reaction
PDU	problem drug users
PR	prevalence ratio
RDS	respondent-driven sampling
Reitox	Réseau Européen d'Information sur les drogues et les Toxicomanies (European Information Network on Drugs and Drug Addiction)
RITA	recent infection testing algorithm
RR	relative risk
SAPI	smartphone assisted personal interviewing
SASI	smartphone assisted self-interviewing
ST9	Standard Table 9
STI	Sexually Transmitted Diseases
TAPI	tablet assisted personal interviewing
TASI	tablet assisted self-interviewing
TDI	treatment demand indicator
TLS	time-location sampling
TSS	temporal spatial sampling
TVS	time, venue sampling
UMHRI	University Mental Health Research Institute, Greece
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNODC	United Nations Office on Drugs and Crime
VDT	venue, day, time sampling
WAPI	web assisted personal interviewing
WB	Western blot
WHO	World Health Organization

Annex 1. Sampling methods — details

The methods to take a sample from a population can be broadly classified as probabilistic and non-probabilistic sampling schemes. The probability sampling as opposed to convenience sampling is a procedure in which each individual from the sampling frame has a defined (known) probability of being included in the sample, although these probabilities do not have to be equal. The advantage of these sampling schemes is that there exist statistical methods to produce an unbiased estimate of the population value together with confidence interval (i.e. estimation of possible random error). However, it may not be appropriate to use statistical methods developed for simple random samples to analyse more complex designs.

1. Traditional probabilistic sampling designs and their application in IDU studies

Random sampling and systematic random sampling

Simple random sample: All individuals in the sampling frame have the same probability of being selected.

- a. The list of individuals in the sampling frame is created. From this list individuals with numbers randomly picked are selected for the study. The numbers are drawn at random by a random numbers generator available in practically all statistical packages.
- b. The list may be available from the beginning or we may assume it will be formed by the order of clients arriving at a certain service/admitted to hospital, etc.
- c. The example of use may be sampling of clients of a drug treatment centre, which can provide a list of patients; or sampling of clients of a service numbered by the order in which they are encountered or arrive at the service premises. Clients with pre-sampled numbers will be invited into the study. As a result a random sample of clients of one service is obtained. If treatment services in a region or country keep a centralised database with identification of individual clients it may be possible to obtain a random sample of clients of services in that region/country.

Systematic random sampling: taking every i^{th} individual

- a. An ordered list of units (clients) is created and the 'sampling interval' i defined (by dividing the number of units in the sampling frame by the desired sample size). The first individual is randomly selected and then starting from this individual every i^{th} individual from the list.
- b. This design can provide biased results in cases where the clients come in 'cycles' in relation to certain characteristics, for example if working clients are scheduled in the afternoon and the cycle of sampling selects always the clients from the morning.

Random or systematic sampling in the field conditions: Recruiting people from open space will not allow a sampling frame to be created beforehand.

- a. To avoid bias from an interviewer selecting a specific type of respondent due to convenience, there are methods of creating a sampling frame directly at the sampled location during the recruitment episode (enumeration).
- b. Enumeration requires the counting of all persons crossing an imaginary line agreed at the beginning of sampling event (line-based enumeration), or entering a defined area (area-based enumeration), depending on the characteristics of the particular sampled location. Alternatively, if members of population are not moving around, the imaginary line is between two interviewers walking across the area (moving line enumeration).
- c. In practice, consecutive members of target group enumerated are approached, depending on the availability of interviewers (for details see (54)).

Cluster sampling and indirect sampling

Cluster sampling: The sample frame contains clusters instead of individuals.

- a. Clusters are generally groups of individuals from the target population who can be found and recruited in one place. It is assumed that each individual belongs to a cluster, but only to one cluster ('fixed population').
- b. Simple random sample or systematic random sample of clusters possibly weighted by the cluster size (probability of selecting a cluster is proportional to the number of target population members associated with the cluster) is taken and all individuals or a sample of individuals from a cluster are invited to a study. A step-by-step guide on how to design cluster sampling is given in (3).
- c. In order to assure a valid cluster sample a relatively large number of clusters should be included. It is recommended that the sample should include at least 30 clusters. This may be not logistically feasible but the aim should be to have a smaller cluster size and larger number of clusters.
- d. An example of clusters is districts/areas of residence. Clusters of a drug using population in treatment (or in contact with services) can be treatment units (including methadone, maintenance services or general practitioners) or other services for drug users (such as accommodation services, low threshold services including needle exchange programmes and outreach activities) at a particular time.

Indirect sampling: In practice a drug user can use more than one service, and so belong to many clusters at the same time, and thus their inclusion probability may be variable depending on the pattern of use of the services. This sampling scheme is, then, better defined as indirect sampling (i.e. we sample from a list of units or individuals that are related to members of our target population in some way which allows to access the members of target population) ^(66, 67).

Multi-stage designs

In practice, due to logistics reasons or practical possibilities of developing a sampling frame, we sample in stages. For example we first sample treatment institutions and then at each unit we take a random sample of patients. Often we also define strata or subgroups to sample from. Such strata can be created, for example, based on geographic location (regions) or characteristics of participants — for example, age groups. Next we sample separately within a stratum.

Implicit stratification may be achieved in systematic random sampling by first sorting the list (sampling frame) by the stratification variable.

2. Sampling schemes specific for hard-to-reach populations

Injecting drug use is often an illegal or stigmatised behaviour and therefore the population is not easily accessible for studies ('hidden'). An exception could be countries where the coverage of services is high, as the majority of the IDU population might attend one or more services, in which case venue-based sampling might be quite sufficient to reach a representative sample of the population. However, in cases of low coverage of services especially in a context of strict anti-drug regulations, the attendance rate to drug treatment and services might be low and other methods would have to be applied in order to recruit an appropriate/representative sample from the population. The estimates relying solely on the institutionalised populations or populations in contact with services are considered biased ^(68, 19, 69). For example, sampling from needle exchange programmes, results in underrepresentation of women, youth and those who have recently started injecting ⁽⁵⁾. In consequence it is not possible to construct a sampling frame and usual probability sampling techniques are less useful ^(70, 19).

All approaches that allow representative sampling of drug users require more or less rigorous formative research before and during designing of the study.

Targeted sampling

Targeted sampling (TS) was first described in (68) to sample injecting drug users directly from the community.

TS requires careful formative research, including a review of existing data and — often very time and resource intensive — ethnographic mapping, to describe key characteristics of the population of interest and well as locations for potential sampling⁽⁷¹⁾. Based on this information quotas are established for each sampling site and demographic characteristic. The exact method of sampling (e.g. systematic, chain referral techniques) for each site and sub-population are then chosen to optimise output.

Targeted sampling — outline procedure:

- 1. Identification of neighbourhoods (geographic areas) where injecting drug use takes place: This can be based on direct observation, interviews with key informants (e.g. drug treatment or harm reduction programme staff, police, hotel desk clerks), reviewing existing data (e.g. police arrest data, emergency room admission data, drug treatment data for residence place).*
- 2. Ethnographic observations of identified neighbourhoods: The aim is to gain insight into social organisation of target groups (in particular the existence of non-overlapping networks), record indicators of intensity of drug injecting (such as used syringes found at location, police activity), other information (social contexts of needle use and needle sharing, drug use profiles, sexual relationship, habits).*
- 3. Sampling of locations: Sampling frame is constructed including the locations (e.g. 3 of the size 3 blocks) within neighbourhoods and the indicators of intensity of drug use, which serve to estimate sampling weights adequate to the expected recruitment yield. Weighted random sample of the locations is then selected (see cluster sampling).*
- 4. Sampling at location: Quotas (desired sample size) are settled for each location based on key population characteristics, for non-overlapping networks. The method for recruitment may be different at each location — for example, snowball technique with seeds in every subgroup identified. Alternatively, interviewers approach all (or a sample depending on the population flow) individuals met during the sampling episode and screen them for eligibility criteria.*
- 5. Adaptation of sampling: The study procedures including recruitment procedures should be altered if the study fails to include some important subgroups.*

Time-location sampling

Time-location sampling (venue, day, time (VDT) sampling, temporal spatial sampling (TSS), Time venue sampling (TVS)) from a methodological point of view is a type of cluster or indirect sampling schemes. If we plan to sample drug users from the community (places where they congregate) we cannot assume that we will always find the same population at a site or venue considered a cluster. Therefore the sampling frame is defined by time intervals at the sites. In order for TLS to be an effective strategy places where drug users congregate must be identifiable and accessible, as well as frequented by the vast majority of the target population. TLS has most often been used to study men who have sex with men but has been used less to study drug users.

Time-location sampling — outline procedure:

1. *Identification of possible venues and sites: As opposed to cluster sampling of clients of services and treatment centres, the places associated with community activities are included. This may be shooting galleries, bars, needle exchange and outreach, parks, areas outside methadone clinics, accommodation services.*
 2. *Formative research: Characterisation of sites and estimating weights. The sites have to be at minimum described in terms of the number of drug users reachable during the selected time unit and the hours when the target population can be found in large enough numbers to make the sampling effort efficient (some initially identified sites will be excluded at this stage). Seasonality in the number of the target population reachable or the structure of population should also be noted (e.g. weekday/weekend, pay days). Weights are developed based on the population size estimated at a given time unit at a given location.*
 3. *Construction of sampling frame ('calendar') and sampling: Sampling frame includes site–time interval units (e.g. day xxx street xxx at 20.00–22.00 and day xxx street xxx at 22.00–24.00 are two different sampling units) in the form of a calendar for the planned study duration. Random, weighted sampling from this 'calendar' is then performed. If different types of locations appear in the sampling frame a stratification procedure might be considered.*
 4. *Sampling at venue/site: The number of respondents sampled at the given time-location unit will either be fixed or dependent on the number of target group members encountered at the site (take-all or take a fixed fraction). Sampling may be systematic, random or convenience.*
-

Design issues

- The choice of time interval for sampling depends on the turnover of population at the identified location. Once the sampling time interval is selected it is the same for all sites in the study. Typically intervals range between 1 and 4 hours. For services a daytime period was also used.
- The same target group member may be encountered by the interviewers at multiple locations. Usually these duplicates are just excluded at the data collection stage (not inviting the person into the study). This could be done by asking a series of non-identifying questions (e.g. sex, birth year, age, race/ethnicity, state of birth, and first two letters of mother's maiden name⁽⁷²⁾).
- Differences in the probability of being included in the sample (i.e. the more places a person attends the more likely he or she is to be recruited into the study). In order to correct for overrepresentation of the most 'active' members of the target population the TLS survey may necessitate weighting at the analysis stage (see Analysis section) and thus the questionnaire should include questions on the frequency of attendance at different services⁽²⁰⁾.

A detailed description of designing TLS surveys, with examples, is provided in (54).

Chain referral sampling schemes

Chain referral techniques (link tracing methodologies, network sampling) rely on the notion that injecting drug users form social networks that might be used to recruit their members into the study. The general idea is that a community member who participates in the study provides information about or recruits his or her network members belonging to the target group and the study follows social 'links' in the target population.

Snowball technique

The snowball technique was developed in the 1950s and 1960s, primarily to study the network structure^(73, 74). In the snowball technique we select seeds who agree to participate in the study. Then we ask them to nominate several people/everyone from their contact network who they think might be interested in taking part in the study and ask for details of how to contact them. The nomination can be provided by giving the names or other identifying information and indicate where this person can be contacted. The study team then randomly selects a pre-specified number or all of the potential participants who are contacted and agree to participate. This procedure continues until the planned sample size is reached or the population is saturated (newly identified contacts already participated in

the study). The drawbacks are uncontrollable non-randomness of the process with oversampling of the 'less hidden' part of the population and unwillingness of the study participants to provide contact details without consent of their peers (^{68, 16, 75}).

Respondent-driven sampling

The respondent-driven sampling is a modification of snowball sampling, and also relies on the social links in the population (^{16, 17}). In respondent-driven sampling the respondents have the additional role of recruiting participants, who are then asked visit the study site.

Respondent-driven sampling — outline procedure:

1. Selection of seeds: Seeds are initial participants of the study. They are non-randomly selected from members of the target population known to the study teams, based on key-informant referrals or through outreach. The number of seeds is variable; many studies use 6–12 seeds.

2. Coupon distribution and peer recruitment: Seeds complete interview and are provided with a defined number of coupons, most commonly 3. They are asked to recruit members of their personal networks who are also members of the target population and to give them one of the coupons. Coupons are typically valid for some defined time period to enter the study. Coupons are numbered in a way that allows recruitment chains to be reconstructed at the time of analysis.

3. Subsequent waves of respondents: Persons who are present at the study site with a valid coupon and meet the eligibility criteria are invited into the study. At the end of the study procedure they are also given the coupons to recruit members of personal network. The respondents recruited by the seeds form the first wave. The respondents recruited by the first wave respondent form the second wave and so on until the desired sample size is reached.

4. Incentives: The respondents are given an incentive for participating in the study at the end of study procedure and also for each recruited person at the end of the time period for which their coupons were valid.

5. Phasing-out: The number of valid coupons distributed to potential respondents has to be carefully monitored. Towards the end of the study, when the total number of respondents is close to the desired sample size the number of coupons distributed to the respondents has to decrease and finally no coupons are distributed.

The participation bias is reduced through a system of dual incentives given as a reward for being interviewed and for recruiting peers to be interviewed, if they show up. Importantly, the possible bias due to different personal network sizes is corrected for at the time of analysis. However, the theoretical assumptions for the RDS sample to be representative of the population might be difficult to meet (⁷⁶).

Although extensive formative research is not required, it may be of value to gain understanding of the community structure, including the existence of disconnected subgroups of subgroups in which participation may be hampered, for example, by cultural or logistical reasons (⁷²).

Detailed instructions how to prepare and conduct RDS study can be found in (25).

Design issues

Seed selection

In the theoretical framework independent of initial seed selection, a representative sample is drawn after the number of waves sufficient to reach so-called equilibrium on pre-specified variables, i.e. the number of waves after which the distribution of those features change by less than 2 % (⁷⁷). There are ways to increase efficiency of reaching equilibrium. First, selection of diverse seeds depending on factors associated with social ties formation (⁷⁸): race/ethnicity/migration, gender/age, drug use/service

use — this is likely to be different in individual settings and should be discussed during the formative research phase (^{79, 80, 81, 82}). Additionally, we are looking for seeds that have some experience in recruiting others, to be able to convince their peer to participate in the study — in this respect active members of the community should be invited as seeds (e.g. from community-based organisations). Other studies suggest that the effectiveness of the seeds (and the subsequent recruitment) can be increased by training each participant (individual or group sessions) (^{83, 78}). Apart from the seeds selection, some suggest using additional incentive for recruiting members of particularly hard-to-reach subgroups (to be defined during the formative research) (^{17, 84}).

Coupon systems

The coupons' numbering system should allow data analysis to take into account the recruitment structure. The simplest way of numbering the coupons given to a responder is to begin with the number of the coupon of the responder and add an extra digit indicating the consecutive number of the coupon. At first consecutive numbers are assigned to the seeds. Then, for example, the three coupons given to seed number 2 will be numbered 21, 22, 23; and the coupons given to the respondent 21 will have numbers 211, 212, 213 and so on. Specific software has been also developed to manage the coupons (RDS Coupon Manager, UCSF Global Health Sciences, San Francisco, USA).

The value of incentive

The incentive has the role of motivating the study participation. The incentives are structures in such a way as to involve peer pressure in the recruitment process (incentive for the recruiter). The value should be high enough to be attractive for the members of target population but not high enough to induce undesirable behaviours, such as selling the coupons to strangers. Studies in developed countries used the value of approximately USD 20–40 and studies in developing countries used USD 2–4 for primary incentive and commonly half of the value for secondary incentive (⁸⁵). The value of the incentive should be discussed during the formative research. Due to legal constraints it is often not possible to distribute monetary incentives, so food coupons, other shopping vouchers, phone cards or other gifts can be used instead.

Study efficiency

When the drug using population is well connected the RDS technique is very efficient in producing the desired sample size. The problems arise when the mean number of network members is small (<20) and when there are strong tendencies for intra-group recruitment (⁸⁶).

Additionally, a study from New York City suggests that the recruitment might not be as efficient in areas with negative attitude towards injecting drug use, although this could be counteracted through RDS training sessions (⁸³).

It was usually possible to recruit the desired sample size of 200–400 in 4 to 12 weeks (⁸⁵).

Barriers to recruitment

Barriers in network penetration may be examined by the recruitment probabilities across different population subgroups and comparison with other data sources (e.g. service data, imprisonment data, infectious disease notifications). Barriers have been identified across geographic area, races and injection drugs (⁸⁷).

Annex 2. Available biological samples and laboratory tests

Possible biological samples

HIV, HCV and HBV tests are best performed on serum/plasma samples that require venepuncture, collection of a blood sample and preliminary processing (e.g. centrifugation). An alternative to venous blood sampling is the collection of capillary blood (dried blood spots, DBS) and tests performed on eluted DBS are as accurate as on venous blood samples^(88, 89, 90). Screening assays are also available from oral fluid and urine samples^(91, 92, 93). The accuracy of non-blood assays, particularly urine assays, is less than the blood assays. Oral fluid testing is established in epidemiological studies of HIV. Less evidence is available for validity of oral samples testing for hepatitis⁽⁹⁴⁾. Results for HCV antibodies have been inconsistent, sometimes showing decreased sensitivity, although this may depend on sampling collection methods and type of laboratory test, and one rapid test has been demonstrated to have good accuracy^(92, 32).

Collection of blood samples, especially through venepuncture, usually requires specific training and is often subject to regulations. This may for example require contracting a trained nurse in the study to take blood samples. This requirement may not be there for DBS or oral fluid but this may differ per country. Information about different samples available is provided in Table 8.

Laboratory based and rapid tests

The standard diagnosis requires transportation of samples to a collaborating laboratory, where the tests are performed. Laboratory test results are usually reported within one to several days. Rapid (point of care) tests are performed directly at the collection site. These are usually immunochromatographic tests and their result can be read visually (discoloured line) in 10–20 minutes from providing a sample for HIV and 20–40 minutes for HCV⁽⁹⁵⁾. Rapid tests may be more expensive than regular laboratory tests. Later on they require confirmation with laboratory test.

The choice of rapid or laboratory based testing will depend on a number of factors including testing settings, available staff (including medically trained staff), available infrastructure (at the testing site, transport arrangements), costs and if the participants are likely to collect the test results⁽²⁹⁾. Attention must also be paid to storage conditions of the kits⁽⁹⁶⁾. National rules and requirements are relevant with regard to rapid tests since they can limit their use to specific situations, settings, professionals or their use can be the subject of specific approval, etc.

In addition to commercially available assays, laboratories may work out other methods or modify commercially available tests that could be used in surveillance studies.

Characteristics of available assays are published by WHO on their Diagnostics and Laboratory Technology website (www.who.int/diagnostics_laboratory/publications/evaluations/en/index.html)⁽⁹⁵⁾.

Table 8 — Biological samples for testing for the infectious disease markers.

Biological material	Collection procedure	Storage conditions	Transport requirements
Whole blood	Venepuncture and collection of 2–5 ml blood into EDTA solution; usually health care worker	Has to be processed to serum samples; <24h in 4°C, 4 weeks at –20°C, if longer storage period –70°C; specimens should be partitioned into small aliquots prior to freezing in order to avoid multiple freeze–thaw cycles.	Dry ice; safe pack
Dried blood spots (capillary blood)	Finger prick (sterile lancet) blood is collected on filter paper and allowed to air dry	Dries in 3 hours at room temperature, dried blood spots may be stored refrigerated (2–8°C), or at room temperature (15–30°C) for 90 days as long as they are not exposed to elevated humidity (>50 %). For long-term storage, dried blood spots may be frozen at –20°C or colder at <50 % humidity.	Plastic bag with desiccant and envelope
Oral fluid	Collected on special device (following manufacturer's instructions); some devices may have limitations with respect to eating, drinking and smoking before sample collection	Usually placed in tube with buffer and may be stored at 2–37°C for a maximum of 21 days from the time of collection, or frozen (–20°C or lower) for 6 weeks. Storage times may vary for different devices.	May be transported in ambient temperature
Urine	Regular collection, any time of day	4°C (must not be frozen) or at room temperature. Should be tested on the same day.	May be transported in ambient temperature

Annex 3. List of indicator sets used internationally

1. EMCDDA, *DRID Guidance Module: Behavioural indicators for injecting drug users*
2. ECDC, Behavioural Surveillance Toolkit
www.ecdc.europa.eu/en/activities/diseaseprogrammes/hash/hiv_behavior_toolkit/Pages/introduction.aspx
3. Global AIDS Response Progress Report
www.unaids.org/en/dataanalysis/knowyourresponse/globalaidsprogressreporting/
4. Dublin Declaration www.indicatorregistry.org/taxonomy/term/2538
5. PAHO/WHO [OPS/OMS] (Pan American Health Organization/World Health Organization) (2008a), 'Encuestas de Comportamiento en Consumidores de Drogas con Alto Riesgo (CODAR). Cuaderno1: Diseño del estudio, adaptación del cuestionario e indicadores' [Behavioural surveys among problem drug users: Questionnaire study design, adaptation of questionnaire and indicators], PAHO/WHO, Washington
(new.paho.org/hq/index.php?option=com_content&view=article&id=689%3aencuestas-decomportamiento-en-consumidores-de-drogas-con-alto-riesgo-codar&catid=1090%3afchiv-pcodar&lang=en).
6. PAHO/WHO [OPS/OMS] (2008b), 'Encuestas de Comportamiento en Consumidores de Drogas con Alto Riesgo (CODAR). Cuaderno2: Manual de entrevista y aplicación del cuestionario' [Behavioural surveys among problem drug users: Questionnaires — interviewer manual], PAHO/WHO, Washington
(new.paho.org/hq/index.php?option=com_content&view=article&id=689%3aencuestas-de47comportamiento-en-consumidores-de-drogas-con-alto-riesgo-codar&catid=1090%3afchiv-pcodar&lang=en).
7. PAHO/WHO [OPS/OMS] (2008c), 'Encuestas de Comportamiento en Consumidores de Drogas con Alto Riesgo (CODAR). Cuaderno3: Cuestionario C-CODAR' [Behavioural surveys among problem drug users: Questionnaires — Questionnaire C-CODAR], PAHO/WHO, Washington
(new.paho.org/hq/index.php?option=com_content&view=article&id=689%3aencuestas-decomportamiento-en-consumidores-de-drogas-con-alto-riesgo-codar&catid=1090%3afchiv-pcodar&lang=en).

Annex 4. Protocol development

A protocol is the document describing all aspects of the study, including the background and rationale, design, study methodology and management as well as statistical considerations for planning and analysis of the data.

- It is developed by the team representing those who will implement the study, which could include those working directly with drug users, epidemiologists/biostatisticians, sociologists, infectious disease clinicians/virologists, representatives of the target group.
- The aim of the protocol is to systematise the study plans, assess feasibility and if the plan (including information to be collected) is consistent with the objectives, assign roles of partners.
- The protocol usually has to be submitted for ethical review.

Protocol outline:

1. Study summary:
 - a. Title, timeframe, funding source, contact details of investigators, list of study sites.
2. Background information and significance:
 - a. Information on existing knowledge based on literature review.
 - b. Description of population to be studied, problems (diseases, behaviours) to be studied, outcomes of prior biological and behavioural studies, any other information useful to understand the problem or choice of study settings.
 - c. Information on compliance with existing regulations, local authorities requirements, partnerships with stakeholders.
3. Objectives and rationale, research question:
 - a. Overriding aims of the study, how important is the problem, what data gaps the study will be addressed, what is the public health significance of the prospective results.
 - b. Detailed description of measureable primary and secondary objectives.
 - c. Discussion of feasibility of achieving the primary objective.
4. Design of the study and methods:
 - a. Study population (target/sampling population definition, inclusion/exclusion criteria, enrolment procedure).
 - b. Study design including the choice of sampling method, main indicators.
 - c. Study instruments (questionnaire, laboratory tests).
 - d. Exact study procedures with description of roles, data collection and storing procedures, biological samples collection, transport and storing procedures, coding, providing laboratory results to respondents.
 - e. Alternative procedures in case of respondent's withdrawal, irregular behaviours etc.
 - f. Procedures for personnel safety, unexpected events procedures.
5. Statistical methods, analysis plan:
 - a. Sample size calculation.
 - b. Detail statistical methods planned for data management and analysis, dummy tables for the main outcomes planned.
 - c. Plan for accounting for missing data, potential biases, sensitivity analysis.
6. Publication and presentation plan:
 - a. Target audience.
 - b. Relevance to the objectives.
7. Ethical considerations.

8. Project management plan:
 - a. Tasks of all people implementing the study.
 - b. Monitoring plans, risks and risk management.
9. Timeline.
10. Budget.
11. References.
12. List of abbreviations.
13. Annexes (if applicable).