Practical guidance to analyse possible cases of HIV-transmission under suppressive cART

The PARTNER Study team

1 Introduction

Based on all the available evidence, the risk of sexual transmission of HIV in the context of fully suppressive combined antiretroviral therapy (cART) is now widely recognised as being effectively zero. Since the publication of the Swiss Statement in 2008, no fully documented case has been published. However, it remains important that HIV clinicians and researchers investigate any future case in which such a transmission is suspected in order to better understand any circumstances in which such a transmission might still occur, if any such circumstances exist. In addition, it is useful to have guidance as to what procedures should be followed before a claim is made of such a transmission having occurred.

Researchers involved in the PARTNER Study have therefore put together this proposed guidance on how to investigate any potential future cases. We hope to share recommendations for how to investigate and analyse such suspected cases including referral to other experts in this field. In this document we propose a protocol for optimal data collection in such cases.

2 Why report individual cases of HIV transmission

Current data on HIV transmission suggests an effectively zero risk of transmission when the HIV positive index partner is on cART with a fully suppressed viral load. While no such case has been observed in any prospective study and the likelihood that such a case might occur in the future is considered extremely low, a single case might still occur under special circumstances.

We regard it as important to standardise our efforts of reporting any potential individual case of HIV transmission under cART. This will allow us to investigate potential risk settings where such a rare cases of HIV transmission might in fact occur.

This document provides a possible guideline on how to collect clinical/epidemiological information and blood samples in order to analyse a possible transmission event from an HIV-positive index partner who is on antiretroviral therapy (cART) with a fully suppressed viral load (<200 copies).

We strongly recommend that any case where a transmission during cART is considered likely after the analysis outlined here, should be submitted for publication in an international peer reviewed journal.

3 Proposed analysis plan in suspected individual cases

In order to investigate the possibility of a sexual transmission during suppressive cART, the following questions will have to be addressed:

1. The similarity and shared ancestry of the viral sequences from the index case and in the newly infected partner
2. The epidemiological circumstances of the possible transmission event including documented HIV testing in the negative partner and VL testing in the positive partner at the start and end of a defined period during which transmission is suspected.
3. The circumstances of the sexual exposure, including a description of other risk factors that might have facilitated non-sexual transmission of HIV (such as use of intra venous-drugs and shared injecting equipment)

Any investigation analysing the possibility of a linked transmission as proposed here, will, of course, have to be conducted with a full informed consent of both partners.

3.1 Molecular link

This is the most important factor to determine if the virus found in the newly infected partner is sufficiently closely related to that of the index partner such that transmission can be assumed to have occurred from the index partner. The analysis of the molecular link (or the exclusion of unlinked viruses) can sometimes be straightforward (e.g. different subtypes detected) but otherwise requires sophisticated analysis results based on standardised, published methodologies in this area and must be interpreted on a case by case basis by experts in the area.

Investigators should try to achieve the following samples from the involved subjects after discussion with the relevant experts who will be conducting the sequencing:

- **All resistance test results** available from the index case and his or her partner
- The last **stored plasma sample** of the index case when viral load was still detectable (> 1000 cps/ml)
- A **PBMC sample** from the **index case**
  The optimal time point for the sample collection is in the 3 months prior to the supposed transmission date. Any sample taken after that date (or at the time of the detection of the suspected transmission case) can be selected.
- A **plasma sample** from the recently infected **partner** (1 ml heparin-plasma) as early as possible after the new HIV-diagnosis or PBMCs for proviral DNA may also be used if the newly infected partner has been rapidly established on ART and is now supressed prior to obtaining a sample.

3.2 Medical history supporting an epidemiological link

A thorough medical and sexual history should be obtained from the index case and the partner. These should be obtained separately. This should include

- History of relationship (rough dates and sexual history).
- Detailed assessment of the time period during which the couples maintained a sexual relationship without the use of condoms. This should include types of sex, including anal and vaginal sex, as well as the presence of sexually transmissible infections.
- Based on these assessments, the time window of possible transmission should be estimated.
- Sexual contacts in addition to the index partner with evaluation of a wider sexual network and contact tracing. This is to cover the possibility that a third person could have been the index case, who may not necessarily have known their HIV status or be on ART.
- Evaluation of the use of chemsex (including slamming) or other intravenous drug use
- The HIV-treatment history of the possible index case including

  - ART treatment dates
  - All available HIV-RNA measurements (especially from the previous two years).
  - Information on drug adherence
- Based on this information the likelihood that the viral load in the index partner was undetectable during the window of possible transmission should be estimated
- Previous anti-HIV negative testing on the newly HIV infected partner

The information required to describe the epidemiological situation might differ for each case and should be detailed to a reasonable degree in order to adequately understand the circumstances.

Tab: **Summary of the required information to analyse a supposed transmission event**

Required information	**From HIV Positive Index Case**	**From Seroconverting Partner**
Clinical history **(Both partners)**	Sexual activity with seroconverting partner Shared drug equipment use STI history HIV viral load ART treatment history	Sexual activity (date/type) Other condomless sex partners (date/type) Chem-Sex (sharing equipment for iv use) History of STIs (in period of possible transmission)
Transmission event	Estimate the defined **period** of time in which the supposed transmission event could have occurred	
Seroconversion		Documentation of last negative and first positive HIV-antibody test
Blood Plasma	If available: last stored sample with detectable viral load >500 copies	Earliest sample available after seroconversion
Viral Load data	Last documented date with HIV-RNA >200cp/ml Frequency of viral load tests during the period of possible transmission	
PBMC	Last available sample after the supposed transmission event	
HIV-Resistance test	Result of last resistance test	Resistance test as soon as possible after seroconversion
HIV treatment	Type of HIV therapy during time period of possible transmission	