Practical research designs for investigating modes of HIV transmission

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“The scientist. He will spend thirty years in building up a mountain range of facts with the intent to prove a certain theory; then he is so happy in his achievement that as a rule he overlooks the main chief fact of all--that his accumulation proves an entirely different thing.”

- Mark Twain, “The Bee Essay”

According to mainstream researchers, penile-vaginal sex drives HIV epidemics in poor countries

Empiric evidence does not support this belief (since 1993: Fumento; Brody; Gisselquist et al.)

No documented case of HIV acquired through penile-vaginal sex in Africa or Asia reported in medical/scientific literature

- **"explained" infections reflect assumptions, not actual evidence**

Medical injections are reliably associated with HIV infection (Gisselquist et al.)

- **possibility of "reverse causation": HIV infected persons seeking medical treatment for symptoms/complications of HIV**

Blood exposures associated with HIV even when reverse causation unlikely:

- medical injections in healthy Zambian women (St. Lawrence et al.)
- tetanus toxoid vaccination in Cameroonian, Kenyan, & Burkina Fasoan women who gave birth in prior 5 years (Deuchert & Brody, Deuchert)
- male and female circumcision in Kenyan, Lesothoan, & Tanzanian virgins and adolescents (Brewer et al.)
- diverse blood exposures in Kenyan children with seronegative mothers (Okinyi et al.)
- blood transfusions in Mozambican children with seronegative mothers (Vaz et al.)

Four elements of a strong research design to determine modes of HIV transmission

1) Comparison between persons with incident infection (within a known interval of time) [cases] and uninfected persons [controls]

2) Comprehensive assessment of both blood and sexual exposures (when, where, why, with whom, & how)

3) Tracing (finding, interviewing, & testing) contacts to these exposures for both cases and controls

4) Sequencing HIV DNA of infected persons' viral isolates (who transmitted to whom)

Best research in mainstream HIV epidemiology has only compared incident cases and controls on generally limited sexual exposures

- **randomized trials of interventions (male circumcision, tenofovir vaginal gel, etc.) similarly limited**

Strongest research to date:

- **repeat testers at a VCT center, in Calabar, Nigeria (Peters et al.)**
  - **blood and sexual exposures assessed fairly thoroughly**
  - **diverse blood exposures associated with incident HIV infection, including those that could not be explained by reverse causation (vaccination, shared razors, medical surgery)**

1) Comparison between persons with incident infection (within a known interval of time) [cases] and uninfected persons [controls]

Need comparison with controls to know whether cases' exposures are unusual in kind or quantity

Recruit participants who have documented repeat HIV tests (for cases, negative → positive):

- **blood donation centers**
- **VCT (HIV testing) centers**
- **medical clinics (especially ANC)**
- **ongoing cohort studies**

Especially valuable: couples who have tested repeatedly and one or both partners are now infected

2) Comprehensive assessment of both blood and sexual exposures

Include anal, vaginal, and oral sex; condom use for each type; details on partners & behaviors with them

Blood exposures in formal and informal healthcare, cosmetic care (e.g., barbering, hairdressing), rituals (e.g., circumcision, scarification), & home settings (e.g., shared razors, syringes)

Tailor to local situation; better to include too many potential types of blood exposure than too few

Collect as specific info as possible on:

- **date**
- **location**
- **provider type**
- **reason for exposure**
- **instruments used**
- **perceptions of hygiene**
- **others involved & roles (exposed?)**

3) Tracing contacts to blood and sexual exposures for both cases and controls

Find, interview, and test persons (contacts) to whom cases & controls have been exposed through sex or blood exposures

- **presented to contacts as a public health service: warning of exposure, chance to get info & testing**

Contacts not known to cases or controls: e.g., exposed in healthcare or cosmetic care

- **search facility/provider records for others seen on same or adjacent days**
- **challenges: no records, no resources for locating**

Known contacts (household members, kin, neighbors, etc.) – easier to find/refer

3) Tracing contacts to blood/sexual exposures (cont.)

Case-contact and control-contact pairs = key units of analysis

- **which exposures with infected contacts associated with transmission (or seropositive concordance) in pairs with at least one infected person**
- **compare cases vs. controls re exposure to infected contacts by exposure type**

Tracing just from cases is inadequate:

- **can't determine whether uninfected persons would have same exposure profiles**
- **slower accumulation of pairs for analysis**
- **fewer exposure types likely to be included**
- **multiple exposure types in pairs limit interpretation**

4) Sequencing HIV DNA of infected persons' viral isolates

Isolating HIV in a person, describing its unique genetic profile, and comparing profiles

Very similar profiles indicate genetically related infections

- **one person transmitted to another, or persons who acquired infection from the same source**

Can use dried blood spots to collect specimens (possibly at time of HIV testing)

Collaboration with laboratory researchers

With sequencing, can trace just spouses (but limits generalizability)

Research design elements crucial for all investigations of HIV transmission

In generalized HIV epidemics, "outbreaks" cannot be identified without all four elements

- **surveillance usually lacking, infections could reflect natural variation**
- **cannot distinguish "old" (prevalent) from "new" (incident) infections**

Outbreak investigations and routine contact tracing for most infectious diseases often do not involve tracing controls' contacts

- **modes of transmission well-established (e.g., TB)**
- **very rare infections**
- **neither situation applies to HIV in poor countries**

Overcoming challenges

Funding? Not available, but probably not necessary

- **most health research in poor countries not funded**
  - **conducted by students, clinicians, professors, & others with no or very small budgets**

Scientific help? It's available

- **I volunteer my time to help with such projects – design, data collection, management, analysis, and writing up results**

What's needed most?

Desire to know what is driving HIV spread in one's community