

Acquisition of Transmitted Drug Resistant HIV-1 Infection Is Associated With The Presence of Sexually Transmitted Infections

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Abstract*

Background: The transmission of drug resistant HIV is concerning as it may compromise the efficacy of subsequent antiretroviral therapy. Resistant viral strains often have a reduced replicative capacity and may also be transmitted less efficiently. However sexually transmitted infections (STIs) have been shown to facilitate HIV acquisition. Hence STIs may facilitate infection by drug resistant viruses that might otherwise not be easily transmissible.

Methods: Cases of primary HIV-1 infection (PHI) from 2000 to 2005 were identified at a single HIV/STI treatment centre. PHI was diagnosed by one or more of the following: negative HIV antibody test within 6 months*, evolving HIV antibody response, negative antibody but positive antigen and/or RNA, or incident infection indicated on the Serological Testing Algorithm for Recent HIV Seroconversion (STARHS). All PHI cases underwent genotypic resistance testing at the time of diagnosis and transmitted drug resistance (TDR) was determined by the presence of one or more primary mutations (IAS 2005). We recorded demographic details and STI diagnoses (gonorrhoea [GC], *Chlamydia trachomatis* [Ct], non-specific urethritis [NSU], primary syphilis [STS], primary genital herpes simplex [HSV] and trichomoniasis [TV]) made at or in the 3 months before* HIV diagnosis. Statistical analysis (Fisher's Exact Test) was performed using SPSS software.

Results: 604 new HIV-1 diagnoses were made between 2000 and 2005. From those we identified 185 cases of PHI (94% male 96% of whom were MSM). 28 (15%) had TDR (17 NRTI, 12 NNRTI, 2 PI and 2 had resistance to 2 or more classes). 124 (67%) underwent STI screening at or within 3 months of diagnosis (68% of TDR, and 67% of wild-type) with one or more STIs diagnosed in 56 (42%) [21 GC, 12 Ct, 27 NSU, 3 STS, 3 HSV, 1 TV]. STIs were seen more frequently in the TDR group (68 vs 31%; p=0.03)

Conclusions: TDR is associated with the presence of STIs. This could be due to STIs facilitating transmission of HIV thereby overcoming fitness barriers. Alternatively it could be explained by an association between risk behaviour, STIs, and poor adherence to antiretrovirals among individuals in sexual networks. Therefore, strategies to improve STI diagnosis and management may decrease TDR as well as overall HIV transmission. The high prevalence of STIs at PHI, alongside the known impact of STIs on genital HIV RNA, supports the need for close cooperation between HIV and STI services for newly infected individuals.

* This abstract contains updated data based on a stricter definition of PHI and timing of STI diagnosis hence differs from that originally submitted

Materials and Methods

- Individuals diagnosed HIV-1 positive between 2000 and 2005 were identified from a database of patients attending a single clinic providing both HIV testing and treatment, and screening for STIs.
- Primary HIV-1 infection (PHI) was diagnosed by one or more of the following:
 - Previous negative HIV antibody test within the last 6 months
 - Evolving HIV antibody response or Western Blot
 - Negative HIV antibody with positive p24 Antigen or HIV RNA
 - Incident infection indicated on the Serological Testing Algorithm for Recent HIV Seroconversion (STARHS) – indicating infection occurred within the last 6 months (Subtype B viruses only)
- Genotypic resistance testing was undertaken at the time of diagnosis on all individuals.
- Genotypes were obtained by population sequencing of the HIV-1 pol gene encompassing the whole protease region and the first 230 codons of reverse transcriptase (RT).
- Transmitted drug resistance (TDR) was defined as the presence of one or more mutations designated on the International AIDS Society (IAS) 2005 list including T215 revertants.
- Isolates containing mutations in the HIV-1 genome associated with significant limitation of viral fitness were identified (Mutations at codon 190, 106 and 215 in RT and 90 in protease)
- Diagnoses of sexually transmitted infections (primary syphilis, gonorrhoea, *Chlamydia trachomatis*, non-specific urethritis, primary genital herpes and trichomoniasis) were recorded if screening had taken place at or in the 3 months before HIV diagnosis. Where more than one STI screen had occurred in that time period the results of the screen closest to HIV diagnosis were recorded.
- Data on sexual risk behaviour (the number of sexual partners and history unprotected anal or vaginal intercourse in the last 3 months) collected from a standardised proforma at the time of initial HIV diagnosis.
- Recreational drug use was recorded where a history was given of regular frequent Cocaine, Ecstasy (MDMA), Methamphetamine, Amphetamine, Heroin or Crack Cocaine use.
- Statistical analysis was carried out using SPSS version 11 software.

Results

- A total of 604 new HIV diagnoses were made between 2000 and 2005.
- Of these 185 cases of PHI were identified. Baseline characteristics are shown below.

| Table 1: Baseline Characteristics | |
|----------------------------------------------------------|---------------------|
| Median age, years (range) | 34 (18 to 65) |
| Gender | |
| Male n (%) | 174 (94%) |
| Female n (%) | 11 (6%) |
| Sexuality | |
| MSM n (% of males) | 169 (96%) |
| Ethnicity | |
| White n(%) | 175 (95%) |
| All others n (%) | 10 (5%) |
| Virological Characteristics | |
| Median First HIV RNA log ₁₀ copies/ml (Range) | 4.99 (20.3 to 6.91) |
| First HIV RNA >1,000,000 n (%) | 32 (18%) |
| Subtype B | 155 (84%) |

- Transmitted Drug resistance (TDR) was found in 28 (15%).
- 17 had mutations conferring resistance to nucleoside reverse transcriptase inhibitors (NRTIs), 12 to Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) and 2 had major Protease Inhibitor (PI) mutations. 2 had resistance to 2 or more classes. (Table 2)

| Table 2: Transmitted Drug Resistance | | | | | |
|--------------------------------------|-------------|--------------------|------------|----------|------------------|
| Subject | RT (NRTI) | RT (NNRTI) | Protease | Subtype | Fitness impaired |
| 1 | M41L | | | B | |
| 2 | M41L, T215D | | | B | Yes |
| 3 | M41L, T215E | K101E, G190A | | B | Yes |
| 4 | M41L, T215E | | | B | Yes |
| 5 | A62V | | | B | |
| 6 | D67N | | | A or B | |
| 7 | T69D, K219Q | A98G, V106A, Y188L | I84V, L90M | B | Yes |
| 8 | T69N | | | B | |
| 9 | T69N, V118I | | | B | |
| 10 | T69N, V118I | | | B | |
| 11 | V118I | | | B | |
| 12 | V118I | | | B | |
| 13 | T215D | | | B | Yes |
| 14 | T215D | | | B | Yes |
| 15 | T215S | | | B | Yes |
| 16 | T215mix | | | B | Yes |
| 17 | K219Q | | | B | |
| 18 | | K103N, V106I | | CRF02_AG | Yes |
| 19 | | K103N, V108I | | B | |
| 20 | | K103N, V108I | | B | |
| 21 | | K103N | | B | |
| 22 | | K103N | | B | |
| 23 | | K103N | | B | |
| 24 | | K103N | | B | |
| 25 | | K103N | | B | |
| 26 | | G190A | | B | Yes |
| 27 | | G190A | | B or D | Yes |
| 28 | | | L90M | B | Yes |

- Screening for sexually transmitted infections was carried out in 124 (67%) - 68% of those with TDR were screened versus 67% of those without TDR. One or more STIs were identified in 56 (45%) - Table 3. Risk behaviour data is shown in Table 4.

| Table 3: Sexually Transmitted Infections | n (%) |
|------------------------------------------|----------|
| Primary Syphilis | 3 (2%) |
| Gonorrhoea | 21 (17%) |
| <i>Chlamydia trachomatis</i> | 12 (10%) |
| Non-Specific Urethritis | 27 (22%) |
| Primary Genital Herpes | 3 (2%) |
| Trichomoniasis | 1 (1%) |
| >1 STI diagnoses | 6 (5%) |

| Table 4: Risk Behaviour | n (%) |
|---------------------------------------------------------------------------|-----------|
| Recreational Drug Use | 45 (24%) |
| Unprotected Anal or Vaginal Sexual Intercourse (UPS) in the last 3 months | 124 (67%) |
| >10 sexual partners in last 3 months | 38 (20%) |

- Using a univariate model, for those who had an STI screen, STIs were significantly more prevalent in the TDR group (68%) than the group with no transmitted resistance (31%) p=0.03 (Fisher's Exact Test)
- In the subgroup with putative fitness impaired virus only 3 had an STI diagnosis compared with 4 in the non-fitness impaired group.
- A multivariable binary logistic regression analysis was undertaken to examine the effect of possible confounding risk behaviour factors (drug use, UPSI and number of sexual partners) on TDR. No significant associations were found for recreational drug use (Odds Ratio 1.30, 95% Confidence Interval 0.38 to 4.32), unprotected sexual intercourse (OR 1.90, 95% CI 0.56 to 6.50) or number of sexual partners (OR 1.01, 95% CI 0.97 to 1.04)

Discussion

- The study demonstrates an extremely high prevalence of acute STIs at or in the three months prior to PHI diagnosis. Although the study does not demonstrate a temporal relationship it is possible that for a number of individuals in this population HIV acquisition was facilitated by a pre-existing STI.
- Moreover, STIs have been shown in a number of studies to increase genital viral shedding⁵. This is particularly concerning in those with PHI at a time when plasma (and genital) viral loads are already extremely high. These factors are likely to facilitate the onward transmission of HIV.
- The prevalence of TDR based on the IAS 2005 definitions was also high in this population (15%). However, this is comparable to other studies of TDR prevalence in those with early HIV infection.
- We have demonstrated in this study a significant association between TDR and acute STIs. This might be explained by a facilitatory effect for viruses with poorer fitness or simply greater risk-taking behaviour in this population.
- There was no correlation between STIs in the TDR group and the presence of mutations putatively associated with reduced viral fitness determined by expert genotypic interpretation. Further formal viral replication / fitness studies are ongoing and may clarify this issue.
- We also did not find an association between recreational drug use and TDR. This may be due to under-ascertainment of drug use, supported by the lower reported use in this population compared with other studies. No relationship was demonstrated for self reported high risk sexual behaviour (unprotected anal or vaginal sexual intercourse) or high rates of partner change.

Conclusions

- In this cohort of predominantly MSM we have demonstrated that TDR is significantly associated with the presence of an acute STI.
- Formal viral replication studies are ongoing to determine whether STIs are providing a facilitatory role in overcoming fitness limitation to enable transmission. However interpretation of genotypic results thus far does not support this.
- We did not find evidence to support recreational drug use or high risk sexual behaviour being independently associated with TDR.
- The high prevalence of STIs in those with recent HIV infection and their effect in increasing viral shedding strongly supports the need for routine STI screening in those newly diagnosed with HIV and the need for close cooperation between HIV and STI services.

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Introduction

- Transmission of drug resistant HIV-1 is a well recognised phenomenon and has been shown to be highly prevalent in the UK¹. National data from UK clinics have shown a year on year increase in the prevalence of transmitted drug resistance (TDR) up to 16% in 2002. Since then the prevalence has decreased but still stands at 9% in 2004².
- TDR is concerning as it is known to be associated with a poorer response to antiretroviral therapy³
- A number of studies have shown associations between use of recreational drugs (particularly methamphetamine), high risk sexual behaviour and HIV acquisition. A recent study has also showed an association with transmitted NNRTI resistance in men who have sex with men (MSM) who recently acquired HIV and who use methamphetamine.⁴ This is thought to be due to poor antiretroviral adherence in drug users coupled with increased sexual disinhibition and risk taking behaviour.
- Mutations of the HIV-1 genome associated with TDR can also adversely affect viral "fitness" - ie. the viral replicative capacity and transmission efficiency.
- Sexually Transmitted Infections (STIs) are known to be associated with HIV acquisition. It is likely that facilitation of transmission occurs by increasing viral shedding in genital secretions, disruption of the genital mucus membrane, and by migration of susceptible inflammatory cells to the site of infection⁵.
- Hence it is possible that a concomitant STI can facilitate not only HIV acquisition *per se* but infection by a resistant strain by overcoming the fitness limitation of the virus.