# HIV drug resistance among people who inject drugs in Eastern Europe and Asia: HPTN 074

Yinfeng Zhang[1], Philip J. Palumbo[1], Jessica M. Fogel[1], Xu Guo[2], William Clarke[1], Paul Richardson[1], Erica L. Hamilton[3], Ngo T. K. Hoa[4], Kostyantyn Dumchev[5], Zubairi Djoerban[6], Irving Hoffman[7], Brett Hanscom[2], William C. Miller[8], and Susan H. Eshleman[1], for the HPTN 074 Study Team

[1] Johns Hopkins University School of Medicine, Baltimore, MD, USA
[2] Fred Hutchinson Cancer Research Center, Seattle, WA, USA
[3] FHI 360, Durham, NC, USA
[4] University of North Carolina Vietnam, Hanoi, Vietnam
[5] Ukrainian Institute on Public Health Policy, Kyiv, Ukraine
[6] University of Indonesia, Jakarta, Indonesia
[7] University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[8] Ohio State University, Columbus, OH, USA

## BACKGROUND

People who inject drugs (PWID) have high HIV incidence and prevalence, and may have limited access to antiretroviral therapy (ART) in some settings. The HIV Prevention Trials Network (HPTN) 074 trial enrolled HIV-infected PWID in Indonesia, Ukraine, and Vietnam and evaluated an intervention that included enhanced support for medication-assisted treatment (MAT) for substance use and ART. The study intervention was associated with reduced mortality and increased viral suppression after 52 weeks of follow-up [1]. In this study, we evaluated baseline HIV drug resistance and antiretroviral (ARV) drug use in HPTN 074.

## METHODS

### STUDY COHORT

HPTN 074 enrolled 502 HIV-infected index participants who met the following inclusion criteria: active injection drug user, HIV viral load ≥1,000 copies/mL, and able to recruit at least one HIV-uninfected network injection partner. Later in the study, index participants were also required to have a CD4 cell count >50 cells/mm$^3$ at screening [1]. The study limited enrollment of individuals who reported prior ART.

### LABORATORY METHODS

HIV drug resistance and ARV drug testing were performed at the HPTN Laboratory Center (Johns Hopkins University, Baltimore, MD, USA). Resistance testing was performed using the ViroSeq HIV-1 Genotyping System v2.0 for samples from index participants with HIV viral loads >400 copies/mL. ARV drug testing was performed using a qualitative, high-throughput assay that detects 20 ARV drugs in five drug classes [2]. The limit of quantification for the assay is 2 or 20 ng/mL, depending on the drug. HIV subtypes were determined by phylogenetic analysis and were confirmed with online subtyping tools.

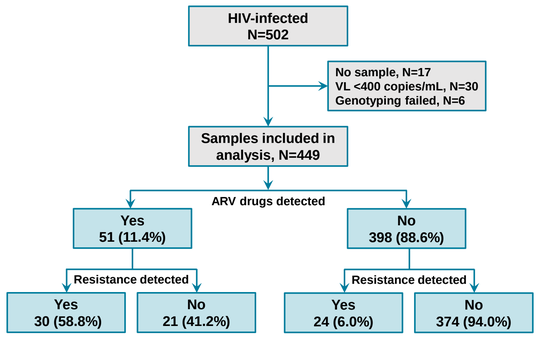
### STATISTICAL METHODS

Logistic regression models were used to assess associations between risk factors and HIV drug resistance.

## RESULTS

### OVERVIEW OF TESTING AND RESULTS

**Figure 1. Study overview.**




### HIV DRUG RESISTANCE TESTING

HIV genotyping results were obtained for 449 (89.4%) of the 502 index participants (Figure 1). HIV drug resistance was detected in 54 (12.0%) of the 449 participants; 29 (53.7%) of the 54 participants had multi-class resistance (non-nucleoside reverse transcriptase inhibitor [NNRTI] + nucleoside/nucleotide reverse transcriptase inhibitor [NRTI] resistance). The most common resistance mutations detected were K103N and M184V.

### ARV DRUG TESTING

ARV drugs were detected in samples from 51 (11.4%) of the 449 participants who had genotyping results; 37 (72.5%) had an NNRTI with one or two NRTIs detected, 10 (19.6%) had an NNRTI detected alone, and two (3.9%) had a boosted protease inhibitor with one or two NRTIs detected. Two participants had an unusual combination of ARV drugs detected (two NNRTIs and one NRTI).

### HIV SUBTYPES

The HIV subtypes were 60.6% CRF01_AE, 36.3% A1, 2.4% unique recombinant forms, and 0.7% B. Participants from Indonesia and Vietnam had mostly subtype CRF01_AE while those from Ukraine had mostly subtype A1.

### FACTORS ASSOCIATED WITH HIV DRUG RESISTANCE

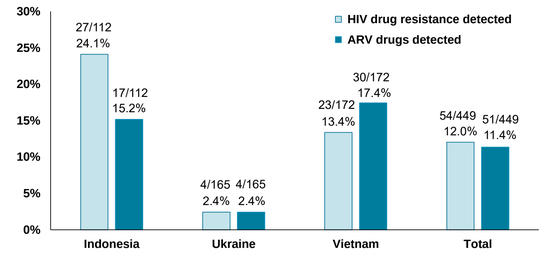
HIV drug resistance was more frequent among those with ARV drugs detected than in those with no drugs detected (58.8% vs. 6.0%; p<0.001, Table 1). Drug resistance was also more frequent among participants in Indonesia (24.1%) compared to Ukraine (2.4%; p=0.001) or Vietnam (13.4%; p=0.014, Figure 2), and among participants who reported a history of incarceration compared to those who did not (42.9% vs. 11.0%; p=0.012).

**Table 1. Factors associated with HIV drug resistance.**

| Variables | HIV resistance N (%) | Adjusted for age and study site | | Multivariate | |
|---|---|---|---|---|---|
| | | aOR (95% CI) | P | aOR (95% CI) | P |
| **HIV viral load (log$_{10}$ copies/mL)[a]** | | 0.68 (0.45, 1.03) | 0.068 | 0.80 (0.48, 1.33) | 0.381 |
| **CD4 cell count (cells/mm$^3$)[b]** | | **0.76 (0.63, 0.90)** | **0.002** | 0.85 (0.69, 1.03) | 0.101 |
| **Antiretroviral drug(s) detected** | | | | | |
| No | 24/398 (6.0%) | Ref | | Ref | |
| Yes | 30/51 (58.8%) | **22.31 (10.12, 49.19)** | **<0.001** | **18.91 (7.86, 45.53)** | **<0.001** |
| **Sex** | | | | | |
| Male | 49/387 (12.7%) | Ref | | | |
| Female | 5/62 (8.1%) | 1.64 (0.52, 5.17) | 0.4 | | |
| **Age** | | | | | |
| 18-29 | 12/77 (15.6%) | Ref | | Ref | |
| 30-39 | 36/295 (12.2%) | 1.07 (0.52, 2.23) | 0.85 | 0.66 (0.27, 1.64) | 0.373 |
| 40-60 | 6/77 (7.8%) | 0.74 (0.25, 2.18) | 0.587 | 0.41(0.10, 1.60) | 0.198 |
| **Study site** | | | | | |
| Indonesia | 27/112 (24.1%) | Ref | | Ref | |
| Ukraine | 4/165 (2.4%) | **0.08 (0.03, 0.24)** | **<0.001** | **0.15 (0.05, 0.48)** | **0.001** |
| Vietnam | 23/172 (13.4%) | **0.50 (0.27, 0.94)** | **0.032** | **0.35 (0.15, 0.81)** | **0.014** |
| **Marital status** | | | | | |
| Married/Partner | 22/221 (10.0%) | Ref | | | |
| Single/Divorced/Separated/Widowed | 32/228 (14.0%) | 1.09 (0.59, 2.02) | 0.775 | | |
| **Education** | | | | | |
| None or primary school | 8/55 (14.5%) | Ref | | | |
| Secondary school | 25/225 (11.1%) | 1.21 (0.50, 2.92) | 0.673 | | |
| Higher education | 21/169 (12.4%) | 0.84 (0.29, 2.39) | 0.741 | | |
| **Injected amphetamines[c]** | | | | | |
| No | 53/390 (13.6%) | Ref | | | |
| Yes | 1/58 (1.7%) | 0.47 (0.05, 4.23) | 0.504 | | |
| **Non-injection stimulant use[c,d]** | | | | | |
| No | 27/298 (9.1%) | Ref | | | |
| Yes | 27/150 (18.0%) | 1.36 (0.68, 2.72) | 0.38 | | |
| **Non-injection opiate use[c,e]** | | | | | |
| No | 49/416 (11.8%) | Ref | | | |
| Yes | 5/32 (15.6%) | 1.28 (0.45, 3.62) | 0.639 | | |
| **Hazardous alcohol use[f]** | | | | | |
| No | 45/298 (15.1%) | Ref | | | |
| Yes | 9/151 (6.0%) | 0.71 (0.32, 1.58) | 0.401 | | |
| **MAT for substance use** | | | | | |
| No | 14/135 (10.4%) | Ref | | | |
| Yes | 40/314 (12.7%) | 1.35 (0.68, 2.68) | 0.397 | | |
| **Number of sexual partners[g]** | | | | | |
| 0 | 29/183 (15.8%) | Ref | | | |
| 1 | 24/240 (10.0%) | 0.78 (0.42, 1.44) | 0.421 | | |
| ≥2 | 1/26 (3.8%) | 0.25 (0.03, 2.01) | 0.193 | | |
| **Number of injection partners[c]** | | | | | |
| 1 | 2/54 (3.7%) | Ref | | Ref | |
| 2-4 | 44/340 (12.9%) | 3.76 (0.86, 16.41) | 0.079 | 3.21 (0.63, 16.43) | 0.162 |
| ≥5 | 8/55 (14.5%) | 2.98 (0.57, 15.54) | 0.194 | 1.72 (0.26, 11.64) | 0.576 |
| **Jail/Prison** | | | | | |
| No | 48/435 (11.0%) | Ref | | Ref | |
| Yes | 6/14 (42.9%) | **3.59 (1.16, 11.12)** | **0.027** | **6.24 (1.49, 26.19)** | **0.012** |

Footnotes: [a]Assessed for increments of log$_{10}$ HIV RNA copies/mL. [b]Assessed for increments of 100 CD4+ cells/mm$^3$. [c]In the past 3 months. [d]Stimulants include cocaine and methamphetamines. [e]Opiates include heroin and opium. [f]Hazardous alcohol use was determined as an AUDIT-C score of ≥4 for males and ≥3 among females. [g]In the past 1 month. Abbreviations: N, number; aOR, adjusted odds ratio; CI, confidence intervals; P, p-value; Ref, reference; MAT, medication assisted treatment.

**Figure 2. HIV drug resistance and ARV drug use by study site.**




### HIV DRUG RESISTANCE AND ARV DRUG USE

Among the 449 participants with test results, 30/449 (6.7%) had ARV drugs and drug resistance detected, 24 (5.3%) had only drug resistance detected, 21 (4.7%) had only ARV drugs detected; and 374 (83.3%) had no drug resistance or ARV drugs detected. Among the 51 with ARV drugs detected, 58.8% had drug resistance. Participants who had ARV drugs detected without resistance were at risk of acquiring resistance to additional classes of ARV drugs.

## CONCLUSIONS

- This study revealed a high prevalence of multi-class resistance among PWID with drug resistance.
- Active ARV use was strongly associated with drug resistance in this cohort of individuals with viral loads >1,000 copies/mL.
- Drug resistance was also associated with study site (Indonesia, greater than Ukraine or Vietnam) and a history of incarceration.

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**RESEARCH COLLABORATORS**
Estelle Piwowar-Manning, Johns Hopkins Univ. School of Medicine, Baltimore, MD, USA
Stephen Hart, Frontier Science Foundation, Amherst, NY USA
Tran Viet Ha, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

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