

# The TREAT Asia Studies to Evaluate Resistance Monitoring Study (TASER-M) - HIV Drug Resistance in the Asia-Pacific

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## Introduction

More than 33 million adults and children were infected with HIV globally at the end of 2008. Access to antiretroviral therapy (ART) in low and middle-income economies increased 10-fold to 4 million people, from 2003 to 2008, providing coverage to 42% of those in need [1].

In Asia, HIV prevalence was 4.7 million in 2008 with new infections ranging from 270 000–410 000. Improvements in regional access have not generally been accompanied by increased viral load or HIV drug resistance (HIVDR) testing [2, 3]. Limited choices of regimen, partnered with ART availability, increases the importance of monitoring HIVDR in the region [4].

Resistance mutations are a major cause of ART failure and resistance to one antiretroviral can result in cross-resistance to other drugs in the same or other drug classes [5, 6, 7]. HIVDR threatens the effectiveness of subsequent ART regimens for the patient and the transmission of drug resistant virus has severe public health consequences [8, 9]. Our study monitors patients for emerging HIVDR following initiation of first- and second-line ART.

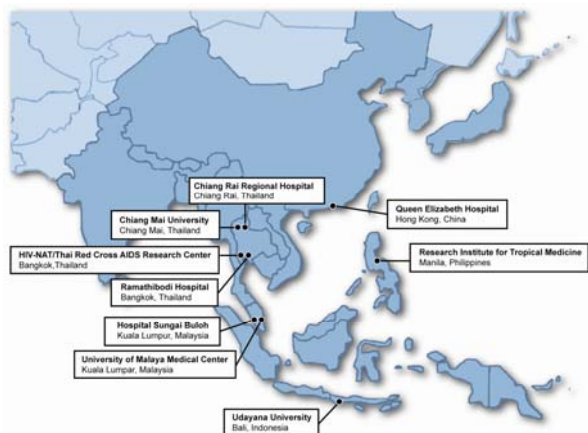


Figure 1. TASER-M clinical sites

## Methods

Eleven sites in 6 countries are collaborating on TASER-M. Participating sites were selected from within the TREAT Asia network based on laboratory capacity to perform genotypic sequencing and the laboratory's participation in the TREAT Asia Quality Assurance Scheme (TAQAS). Sites are government/university-based clinics and hospitals or private clinics in major cities and urban areas. Nine sites submitting data in March 2009 are shown in Figure 1.

Using a prospective, multi-centre interval cohort design with sequential enrollment, up to 240 participants per clinical centre (11 centres over 4 years) are being recruited. Assuming enrollment includes 90% naive patients and the observed proportions of HIVDR at 12 months are 5%, 10% or 15%, the study is powered to discriminate HIVDR at 12 months in naive and experienced patients to within +/- 1-2% and +/- 2%-5%, respectively.

## Results

In March 2009, 7 sites (Thailand, Hong Kong, Malaysia) provided genotypic data for 718 naive (96.5%) and experienced (3.5%) patients.

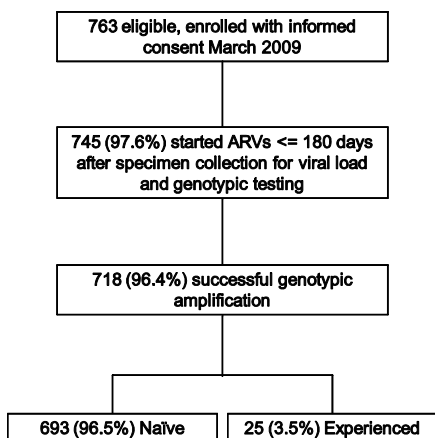


Figure 2. Flow chart of TASER-M patients

### Naive patients

Baseline characteristics are shown in Table 1. Of first-line regimens, 85.6% were based on non-nucleoside RT inhibitors (NNRTIs), nevirapine (56% more commonly prescribed than efavirenz (42%). Protease inhibitor (PI) regimens were prescribed for 10.5% of patients, mainly based on atazanavir (43%) or lopinavir (LPV) (41%).

Table 1. Baseline characteristics of naive patients

Naive Patients	n = 693
Age (years)	Median (IQR) 36.5 (31.1-43.2)
Baseline HIV-1 viral load (copies/mL)	100 000 (44 016-237 012)
Baseline CD4 count (cells/μL)	99 (33.5-201)
Gender	
Male	454 (65.5)
Female	239 (34.5)
HIV Exposure	
Heterosexual contact	520 (75)
Homosexual contact	128 (18.5)
Other*	45 (6.5)
CDC classification	
Category A	296 (42.7)
Category B	152 (21.9)
Category C	245 (35.4)
First HAART regimen	
HAART-NNRTI	593 (85.6)
HAART-PI	73 (10.5)
HAART-NRTI	24 (3.5)
HAART-NNRTI/PI	3 (0.4)

\* The HIV exposure category "Other" includes injecting drug users (IDUs), patients infected by blood products and unknown exposures.

For naive patients, both PR and RT regions of the HIV genome were successfully amplified in 683 (98.6%) specimens. Either PR or RT was amplified in 8 (1.2%) and 2 (0.3%) samples, respectively. Circulating recombinant forms (CRFs), the result of recombination between subtypes within a dually infected person, are constantly emerging and subtypes and CRFs are differentially distributed globally [12]. As shown in Table 2, most subtypes were CRF01\_AE (79.9%) or subtype B (15.6%). Non-CRF01\_AE recombinants were identified in 10 (1.3%) patients. For 20 (2.7%) patients, the subtype sequenced from PR and RT differed.

Table 2. Naive patient subtypes and CRFs by country

n (%)	Total	Thailand	Hong Kong	Malaysia
693	510 (73.6)	108 (15.6)	75 (10.8)	
A1	1 (0.1)	1 (0.2)	-	-
A1/C	1 (0.1)	-	1 (0.9)	-
B	108 (15.6)	34 (6.7)	55 (50.9)	19 (25.3)
B/CRF01_AE	5 (0.7)	1 (0.2)	-	4 (5.3)
C	3 (0.4)	-	2 (1.9)	1 (1.3)
C/CRF01_AE	2 (0.3)	2 (0.4)	-	-
D/B	1 (0.1)	1 (0.2)	-	-
D/CRF01_AE	2 (0.3)	2 (0.4)	-	-
K/CRF01_AE	3 (0.4)	2 (0.4)	-	1 (1.3)
CRF01_AE	554 (79.9)	457 (89.6)	49 (45.4)	48 (64)
CRF01_AE/B	3 (0.4)	2 (0.4)	-	1 (1.3)
CRF02_AG	1 (0.1)	1 (0.2)	-	-
CRF02_AG/G	1 (0.1)	-	-	-
CRF03_AB	3 (0.4)	3 (0.6)	-	-
CRF07_BC	3 (0.4)	2 (0.4)	1 (0.9)	-
CRF07_BC/B	2 (0.3)	2 (0.4)	-	-

### Experienced patients

For the 25 (3.5%) experienced patients, median age was 36.5 years (IQR: 32.4 - 41.9), most were female (64%) and HIV exposure was predominantly heterosexual (92%). Sixty percent of patients reported at least one CDC class C event, pre-TASER-M. Of 21 patients with CD4 counts ≤ 6 months prior to second-line therapy, the median CD4 count was 197 (IQR: 109 - 299). Median baseline HIV RNA was 10 680 copies per ml (IQR: 3782 - 34 452). Failed first-line regimens were NNRTI-based (median duration = 30.3 months). Second-line regimens were PI-based, 88% on LPV. All 25 specimens had PR and RT regions successfully amplified; 21 (84%) were CRF01\_AE, 3 were subtype B and 1 patient was CRF03\_AB.

## Conclusions

TASER-M will provide estimates of the prevalence and incidence of primary (naive) or secondary (experienced) HIVDR. Some studies suggest differential effects of HIVDR mutations according to subtype and subtype-specific selection of mutations for antiretroviral drugs [11, 12]. In TASER-M, most patients have non-B subtypes and patient genotypic data has a well characterised ARV history. Opportunities exist to investigate the impact of drug resistance on rates of HIV disease progression and response to treatment in non-B subtypes.

## References

- WHO. Towards universal access: scaling up priority HIV/AIDS interventions in the health sector: progress report 2009.
- UNAIDS. AIDS epidemic update: November 2009.
- Cohen GM. Access to diagnostics in support of HIV/AIDS and tuberculosis treatment in developing countries. AIDS. 2007 Jul 21;21(14):1881-7.
- Bennett DE, Bertagnoli S, Sutherland D, Gilks CF. The World Health Organization's global strategy for prevention and assessment of HIV drug resistance: Antiretroviral therapy. 2008;13 Suppl 2:1-13.
- Waldauer A, Vondrasek J. Inhibitors of HIV-1 protease: a major success of structure-assisted drug design. Annual review of biochemistry and biophysics. 1998;27:249-84.
- Johnson VA, Bragg-Verzer E, Cloer B, Gumbart HF, Karickhoff DR, Pillay D, et al. Update of the Drug Resistance Mutations in HIV-1. Spring 2008. Top HIV Med. 2008 Mar-Apr;16(1):62-8.
- Yip SH, Sheen CW, Fahey J, Ziani M, Tyson D, Lima VD, et al. N348I in the connection domain of HIV-1 reverse transcriptase confers zidovudine and nevirapine resistance. J Virol. 2007 Dec;81(24):13355.
- Pilly D, Basaran K, Juraans S, Prins M, Masqueler B, Dabis F, et al. The impact of transmitted drug resistance on the natural history of HIV infection and response to first-line therapy. AIDS (London, England). 2005 Jan 2;20(1):21-8.
- Kierthiratana S, Sungkanuparph S. Emerging of HIV drug resistance: epidemiology, drug resistance, treatment and prevention. Current HIV research. 2009 May;7(3):273-8.
- Kijak GL, McCauley FE. HIV diversity, molecular epidemiology, and the role of recombination. Current infectious disease reports. 2005 Nov;7(6):480-8.
- Martinez-Cajas JL, Past-Pai N, Klein MB, Wainberg MA. Role of genetic diversity among HIV-1 non-B subtypes in drug resistance: a systematic review of virologic and biochemical evidence. AIDS reviews. 2008 Oct-Dec;10(4):212-23.
- Shafer RW, Schapiro JM. HIV-1 drug resistance mutations: an updated framework for the second decade of HAART. AIDS reviews. 2008 Apr-Jun;10(2):67-84.

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