

Executive Summary

Project Title:

Development of genotyping test for improving the clinical antiretroviral treatment on Integrase inhibitor and CCR5 antagonist in Hong Kong (MSS180R)

Objectives:

This project has 5 major objectives:

1. Develop a new and cost effective genotyping resistance test to monitor drug resistance related mutations in the protease, reverse transcriptase and integrase region of *pol* gene and V3 region of *env* gene
2. Investigate a genotyping method to determine the HIV-1 tropism and estimate the prevalence of HIV-1 CCR5 variants among various genotypes prevalent in Hong Kong
3. Perform surveillance monitoring of the presence of primary resistance HIV-1 isolates to integrase inhibitor and CCR5 antagonist in our community
4. Evaluate the development of drug resistance related mutations through longitudinal monitoring after initiation of ordinary HAART plus integrase inhibitor or CCR5 antagonist
5. Build up a database on primary resistance mutations to integrase inhibitor and CCR5 antagonist and the HIV-1 tropism among various HIV-1 genotypes prevalence in Hong Kong

Design and Setting:

A longitudinal study of 3 years was proposed for plasma samples collected from 400 local HIV-1 infected patients requesting for genotyping resistance test between 2010 and 2013. Multiple samples were also collected every 6 months for longitudinal monitoring or sample at any time when patient showing clinical failure symptoms. The protease/reverse transcriptase/integrase region of HIV-1 *pol* gene and gp120 and gp41 region of *env* gene were sequenced. The sequences were then analyzed on web-based algorithms, including Stanford HIV drug resistance database, Geno2Pheno and WebPSSM to identify drug resistance related mutations in *pol* gene, *int* gene and tropism in *env* gene.

Participants:

In this 3-year study, a total of 1150 samples from 400 HIV-1 patients were collected from Integrated Treatment Centre (Department of Health). The patient background and treatment history was blinded which patient privacy will not be disturbed.

Interventions:

This project provided the first comprehensive set of surveillance data in Hong Kong for the newly-approved antiretrovirals integrase inhibitor and CCR5 antagonist.

Main Outcome Measures:

During the 3-year study, a low-cost in-house assembled assay was successfully evaluated to monitor drug resistance mutations in the protease, reverse transcriptase and integrase region of *pol* gene and V3 region of *env* gene.

Results:

In summary, protease inhibitor resistance mutations were most common, followed by nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors. There was no temporal trend of increase in resistance. Integrase major resistance mutations were identified in two CRF01_AE raltegravir-treated patients but none in raltegravir-naïve patients. Integrase minor resistance mutations were observed in both HIV-1 subtype B and CRF01_AE-infected patients. The prevalence of dual/mixed- or X4-tropic virus in treatment-naïve CRF01_AE patient was 39.1%, which was significantly higher than subtype B patient ($P < 0.05$), regardless of the choices of genotypic algorithms. The phenotypic data also proposed a better genotypic tropism prediction of HIV-1 CRF01_AE with the use of both Geno2pheno (FPR = 10%, Clonal) and WebPSSM (x4r5 subtype B matrix) algorithms in combination. The sensitivity and specificity for this combination were 88.9% and 89.3%, respectively.

Conclusions:

Throughout this project, a simple and cost-effective genotyping resistance test was developed. The transmitted HIV-1 drug resistance was uncommon for antiretroviral therapy in Hong Kong for this period. No integrase resistance mutation was detected in integrase inhibitor-naïve patients. The high prevalence of dual/mixed- or X4-tropic virus in CRF01_AE demonstrated the need for special attention to future treatment strategies.

Publications:

1. Chen JH, Wong KH, Chan KC, To SW, Chen Z, Yam WC. Phylodynamics of HIV-1 subtype B among the men-having-sex-with-men (MSM) population in Hong Kong. *PLoS One* September 22, 2011

2. Chen JH, Wong KH, Li PC, Chan KK, Kee MP, To SW, Yam WC. In-house HIV-1 genotype resistance testing to determine highly active antiretroviral therapy resistance mutations in Hong Kong. *Hong Kong Med J* 2012 Feb;18(1):20-4
3. To SW, Chen JH, Yam WC. Current assays for HIV-1 diagnostics and antiretroviral therapy monitoring: challenges and possibilities. *Future Virology* 2013 Apr;8(4):405-419
4. To SW, Chen JH, Wong KH, Chan KC, Chen Z, Yam WC. Determination of the high prevalence of Dual/Mixed- or X4-tropism among HIV type 1 CRF01_AE in Hong Kong by genotyping and phenotyping methods. *AIDS Res Hum Retroviruses* 2013 Aug;29(8):1123-8
5. To SW, Chen JH, Wong KH, Chan KC, Ng HM, Wu H, Lam JT, Yam WC. Performance comparison of an in-house integrase genotyping assay versus the ViroSeq™ Integra48, and study of HIV-1 integrase polymorphisms in Hong Kong. *J Clin Virol* 2013 Sep;58(1):299-302

Conferences:

1. To SW, Chen JH, Yam WC. Study of HIV-1 CRF01_AE Integrase region in Hong Kong. 16th Research Postgraduate Symposium, 7th – 8th December 2011, Faculty of Medicine, The University of Hong Kong
2. To SW, Chen JH, Yam WC. High prevalence of CXCR4 in HAART-naïve HIV-1 CRF01_AE-infected patients. 10th European Meeting on HIV & Hepatitis – Treatment Strategies & Antiviral Drug Resistance, 28th – 30th March 2012, Virology Education, Barcelona, Spain
3. Chen JH, To SW, Yam WC. The spreading of new generation HIV-1 recombinant forms in the metropolitan city. 10th European Meeting on HIV & Hepatitis – Treatment Strategies & Antiviral Drug Resistance, 28th – 30th March 2012, Virology Education, Barcelona, Spain
4. Yam WC, To SW, Chen JH. Rapid development of raltegravir resistance in a CRF01_AE-infected patient. 10th European Meeting on HIV & Hepatitis – Treatment Strategies & Antiviral Drug Resistance, 28th – 30th March 2012, Virology Education, Barcelona, Spain
5. To SW, Chen JH, Yam WC. The spread of minority HIV-1 strains in Hong Kong. 18th International Bioinformatics Workshop on Virus Evolution and Molecular Epidemiology, 25th – 30th August 2013, University of Florida, USA
6. To SW, Chen JH, Yam WC. Genotyping and phenotyping study of HIV-1 tropism in Hong Kong. 18th Research Postgraduate Symposium, 11th – 12th December 2013, Faculty of Medicine, The University of Hong Kong