

Host Genetic Factors Influencing Drug Disposition and Response to HIV treatment

Final Report

Patients receiving combination (≥ 3 drugs) anti-retroviral therapy (ART) were recruited from either cohorts prospectively followed up (eg UK Collaborative HIV Cohort; CHIC) or else case-controlled from well characterised patient populations. Main endpoint measures were drug exposure and/or response (as measured by plasma HIV viral load). The following genes were examined:

Drug metabolism:	eg in CYP P450 isoforms, nuclear transcription factors, phase II enzymes.
Drug transporters:	eg MDR1 (P-gp), MRP-1, MRP-2, MRP-5, MRP-7, SLCOs.
Protein binding:	affecting unbound concentrations of drug
Target receptors	affecting clinical response or toxicity

Major findings:

- i) We have reported significant pharmacogenetic influences on drug exposure for HIV drugs (lopinavir, nevirapine, tenofovir, atazanavir, efavirenz)
- ii) we have combined these data into mathematical models of pharmacokinetics, which also include environmental effects such as weight, ethnicity, gender, drug interactions
- iii) we have leveraged cofunding from the MRC, NIHR and other funders to extend our pharmacogenetics work, much of which was based on, or was an extension of this project.

Primary Research Publications

1. Sarfo FS, Zhang Y, Egan D, Tetteh LA, Phillips R, Bedu-Addo G, Sarfo MA, Khoo S, Owen A, Chadwick DR. Pharmacogenetic associations with plasma efavirenz concentrations and clinical correlates in a retrospective cohort of Ghanaian HIV-infected patients. *J Antimicrob Chemother.* 2013 Sep 29. PMID: 2408049
2. Siccardi M, Marzolini C, Seden K, Almond L, Kirov A, Khoo S, Owen A, Back D. Prediction of drug-drug Interactions Between Various Antidepressants and Efavirenz or Boosted Protease Inhibitors Using a Physiologically Based Pharmacokinetic Modelling Approach. *Clin Pharmacokinet.* 2013 Mar 12. PMID: 23479398
3. Carr DF, Chaponda M, Jorgensen AL, Castro EC, van Oosterhout JJ, Khoo SH, Lalloo DG, Heyderman RS, Alfirovic A, Pirmohamed M. Association of Human Leukocyte Antigen Alleles and Nevirapine Hypersensitivity in a Malawian HIV-Infected Population. *Clin Infect Dis.* 2013 May;56(9):1330-9. doi: 10.1093/cid/cit021 PMID: 23362284
4. Schipani A, Egan D, Dickinson L, Davies G, Boffito M, Youle M, Khoo SH, Back DJ, Owen A. Estimation of the effect of SLCO1B1 polymorphisms on lopinavir plasma concentration in HIV-infected adults. *Antivir Ther.* 2012 Apr 4. doi: 10.3851/IMP2095. PMID: 22477
5. Liptrott NJ, Pushpakom S, Wyen C, Fätkenheuer G, Hoffmann C, Mauss S, Knechten H, Brockmeyer NH, Hopper-Borge E, Siccardi M, Back DJ, Khoo SH, Pirmohamed M, Owen A; on behalf of the German Competence Network for HIV/AIDS. Association of ABCC10 polymorphisms with nevirapine plasma concentrations in the German Competence Network for HIV/AIDS. *Pharmacogenet Genomics.* 2012 Jan;22(1):10-19
6. Pushpakom SP, Liptrott NJ, Rodríguez-Nóvoa S, Labarga P, Soriano V, Albalater M, Hopper-Borge E, Bonora S, Di Perri G, Back DJ, Khoo S, Pirmohamed M, Owen A. Genetic variants of ABCC10, a novel tenofovir transporter, are associated with kidney tubular dysfunction. *J Infect Dis.* 2011 Jul;204(1):145-53
7. Schipani A, Wyen C, Mahungu T, Hendra H, Egan D, Siccardi M, Davies G, Khoo S, Fätkenheuer G, Youle M, Rockstroh J, Brockmeyer NH, Johnson MA, Owen A, Back DJ; on behalf of the

- German Competence Network for HIV/AIDS. Integration of population pharmacokinetics and pharmacogenetics: an aid to optimal nevirapine dose selection in HIV-infected individuals. *J Antimicrob Chemother*. 2011 Jun;66(6):1332-1339. Epub 2011 Mar 25.
8. Schipani A, Siccardi M, D'Avolio A, Baietto L, Simiele M, Bonora S, Rodríguez Novoa S, Cuenca L, Soriano V, Chierakul N, Saguenwong N, Chuchuttaworn C, Hoskins JM, Dvorak AM, McLeod HL, Davies G, Khoo S, Back DJ, Di Perri G, Owen A. Population pharmacokinetic modelling of the association between 63396C>T Pregnane X Receptor polymorphism and unboosted atazanavir clearance. *Antimicrob Agents Chemother*. 2010 Dec;54(12):5242-50. PMID:20921307
 9. Hartkoorn RC, Kwan WS, Shallcross V, Chaikan A, Liptrott N, Egan D, Sora ES, James CE, Gibbons S, Bray PG, Back DJ, Khoo SH, Owen A. HIV protease inhibitors are substrates for OATP1A2, OATP1B1 and OATP1B3 and lopinavir plasma concentrations are influenced by SLCO1B1 polymorphisms. *Pharmacogenet Genomics*. 2010 Feb;20(2):112-20.
 10. Stöhr W, Back D, Dunn D, Sabin C, Winston A, Gilson R, Pillay D, Hill T, Ainsworth J, Gazzard B, Leen C, Bansi L, Fisher M, Orkin C, Anderson J, Johnson M, Easterbrook P, Gibbons S, Khoo S; on behalf of the UK CHIC Steering Committee. Factors influencing lopinavir and atazanavir plasma concentration. *J Antimicrob Chemother* 2010 Jan;65(1):129-37.
 11. Mahungu T, Nair D, Smith CJ, Egan D, Youle M, Johnson MA, Khoo SH, Back DJ, Owen A. The Relationships of ABCB1 3435C>T and CYP2B6 516G>T With High-Density Lipoprotein Cholesterol in HIV-Infected Patients Receiving Efavirenz. *Clin Pharmacol Ther*. 2009 Aug;86(2):204-11
 12. Rodríguez-Nóvoa S, Labarga P, Soriano V, Egan D, Albalater M, Morello J, Cuenca L, González-Pardo G, Khoo S, Back D, Owen A. Predictors of Kidney Tubular Dysfunction in HIV-Infected Patients Treated with Tenofovir: A Pharmacogenetic Study. *Clin Infect Dis*. 2009;48:e108-116
 13. Mahungu T, Smith C, Turner F, Egan D, Youle M, Johnson M, Khoo S, Back D, Owen A. Cytochrome P450 2B6 516G-->T is associated with plasma concentrations of nevirapine at both 200 mg twice daily and 400 mg once daily in an ethnically diverse population. *HIV Med*. 2009;10:310-17
 14. Siccardi M, D'Avolio A, Baietto L, Gibbons S, Sciandra M, Colucci D, Bonora S, Khoo S, Back D, Di Perri G, Owen A. Association of a single nucleotide polymorphism in pregnane-X-receptor (PXR 63396C>T) with reduced concentrations of unboosted atazanavir. *Clin Infect Dis* 2008;47(9):1222-5
 15. Stöhr W, Back D, Dunn D, Sabin C, Winston A, Gilson R, Pillay D, Hill T, Ainsworth J, Pozniak A, Leen C, Bansi L, Fisher M, Orkin C, Anderson J, Johnson M, P, Sara Gibbons S, Khoo S. Factors Influencing Efavirenz and Nevirapine Plasma Concentration: Effect of Ethnicity, Weight, and Co-Medication. *Antivir Ther* 2008;13:675-85
 16. Wyen C, Hendra H, Vogel M Hoffmann C, Knechten H, Brockmeyer N, Bogner J, Rockstroh J, Esser S, Jaeger H, Harrer T, Mauss S, Lunzen J, Skoetz N, Jetter A, Groneuer C, Fätkenheuer G, Khoo S, Egan D, Back D, Owen A. Impact of CYP2B6 983T>C polymorphism on NNRTI plasma concentrations in HIV-infected patients. *J Antimicrob Chemother* 2008;61(4):914-8

Reviews

1. Else LJ, Taylor S, Back DJ, Khoo SH. Pharmacokinetics of antiretroviral drugs in anatomical sanctuary sites: the male and female genital tract. *Antiviral Therapy* 2011; 16:1149-1167. PMID: 22155899
2. Else LJ, Taylor S, Back DJ, Khoo SH. Pharmacokinetics of antiretroviral drugs in anatomical sanctuary sites: the fetal compartment (placenta and amniotic fluid). *Antiviral Therapy* 2011; 16:1139-1147. PMID: 22155898
3. Owen A, Khoo SH. Pharmacogenetics of antiretroviral agents. *Curr Opin HIV AIDS*. 2008 May;3(3):288-95.
4. Khoo S. HIV and Pharmacogenomics in 2007. *Pharmacogenomics*. 2007 Jan;8(1):25-7.
5. Owen A, Pirmohamed M, Khoo S, Back DJ. Pharmacogenetics of HIV Therapy. *Pharmacogenetics and Genomics* 2006;16:693-703

Dissemination

In addition to presentation at major international scientific conferences (CROI, International AIDS Society meetings, International HIV PK Workshop) and peer-reviewed journals, we have outlined our work in our website (www.hiv-druginteractions.org) and through the NIHR Biomedical Research Centre undertaken lectures and arts-based projects across 5 Merseyside schools.

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