Institution:
UNIVERSITY OF LIVERPOOL and LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Unit of Assessment:
UOA1 - Clinical Medicine

Title of case study:
Therapeutic Drug Monitoring for HIV drugs

1. Summary of the impact

The University of Liverpool (UoL) was the first to identify the potential role for Therapeutic Drug Monitoring (TDM) for HIV drugs (1994) and was at the forefront of describing use of ritonavir as a pharmacoenhancer to boost drug concentrations (1997); now the standard of care globally for HIV protease inhibitors. The work has steered TDM's incorporation into treatment guidelines in the UK and Europe. In 2008 TDM was adopted by US guidelines. Since then, we have developed TDM interpretation through use of population modelling, with uptake from UK and European providers; 4,000 patients in the UK benefit each year from safe and effective dosing as a result. This work is led by Professors DJ Back and SH Khoo, with additional contributions from Prof A Owen (2008 onwards) and Dr M Siccardi (2012 onwards).

2. Underpinning research

In 1994 the UoL started measuring HIV drug concentrations, and in 1999, acquired mass spectrometry (supported by MRC funding) allowing high throughput assays and highly sensitive measurement of drugs in plasma, cells and compartments. This capability supported basic science, clinical and epidemiological studies through an expanded repertoire of drug analysis (to cover all licensed HIV drugs), to measure drug concentrations in putative sanctuaries such as the genital tract, tissue, CNS, across the placenta, breast milk and inside cells. Examples of these studies included two UK Dept of Health grants to study TDM (including one of only a few randomised controlled trials in 2006), and a Gates funded study into use of HIV drugs to prevent infection in exposed individuals (2012).

The UoL established a TDM service in 1999, and by 2005 this had grown to become a national reference laboratory undertaking 4,500 tests/year across >100 NHS Trusts, with a revenue of >£400,000. CPA accreditation was successfully acquired for the TDM programme in 2003, and GCLP accreditation since 2010. By this time the UoL was also undertaking TDM for the Republic of Ireland, Scandinavia, Israel and Singapore. In 2005 the TDM service was spun into Delphic Diagnostics Ltd, and in 2009 this service was acquired by Lab21. The UoL has a supporting programme of research around TDM, including development of new assays and semi-automated reporting algorithms, use of population pharmacokinetic modelling for predicting exposure and integration of drug levels with resistance data. In addition to developing the analytical techniques, the UoL developed algorithms, rules and models which allow the interpretation of that drug concentration, depending on the clinical context, and time of sampling. The UoL was one of the earliest to conduct an RCT of TDM vs standard of care (the POPIN Study) [7].

A key area for TDM has been optimising Protease Inhibitor (PI) concentrations. The UoL published the first report of the use of ritonavir as a pharmacoenhancer or booster of other PIs in HIV+ patients [Merry et al, AIDS 1997]. This became, and remains the standard of care for PI therapy, yet variability in drug concentrations achieved remained a challenge and was a key factor in use of TDM in selected patients. The research has shown how to optimally manage the use of ritonavir, alone or with other PIs, thereby benefiting patient health and increasing the cost-effectiveness of treatment.

The UoL's research and its impact are integrally linked: MRC and Dept of Health/NIHR funding established bioanalytical capability so that early clinical studies could be undertaken leading to the implementation of TDM into UK Treatment Guidelines since 2003. Approximately £5.8m of research funding from Wellcome, MRC, EPSRC, NIHR, Gates and industry grants to the University of Liverpool have been supported by this capability. Conversely, large datasets (>20,000 measurements) within the UoL's TDM Registry have supported its research through validation of population pharmacokinetic (and pharmacogenetic) models, and enabled the successful award and completion of a Wellcome Programme in PK-PD modelling (PKPDia; PI: Khoo).

3. References to the research

1. **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 Citations: 20 Impact Factor: 5.848

2. 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 Citations: 87 Impact Factor: 9.374

3. **Else LJ**, Jackson A, Puls R, **Hill A**, Fahey P, Lin E, **Amara A, Siccardi M, Watson V, Tjia J**, Emery S, **Khoo S**, **Back DJ**, Boffito M. Pharmacokinetics of lamivudine, and lamivudine-triphosphate after administration of 300 mg and 150 mg once-daily to healthy volunteers. The ENCORE 2 Study. *Antimicrob Agents Chemother*. 2011 Dec 19. PMID: 22183172 Citations: 5 Impact Factor: 4.565

4. Pollock L, **Else L,** Poerksen G, Molyneux E, Moons P, Walker S, **Fraser W, Back D**, **Khoo S**. Pharmacokinetics of nevirapine in HIV-infected children with and without malnutrition receiving divided adult fixed-dose combination tablets. *J Antimicrob Chemother*. 2009 Dec;64(6):1251-9. Citations: 14 Impact Factor: 5.338

5. 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, **Gibbons S**, **Khoo S**. Factors Influencing Efavirenz and Nevirapine Plasma Concentration: Effect of Ethnicity, Weight, and Co-Medication. *Antivir Ther* 2008;13:675-85 Citations: 47 Impact Factor: 3.073

6. Boffito M, Jackson A, **Amara A, Back D**, **Khoo S**, Higgs C, Seymour N, Gazzard B, Moyle G. Pharmacokinetics of darunavir/ritonavir and atazanavir-ritonavir once daily over 72 hours following drug cessation. *Antimicrob Agents Chemother.* Sep;55(9):4218-23. Epub 2011 Jun 27. PMID:21709075 Citations: 4 Impact Factor: 4.565

7. **Khoo SH**, Lloyd J, Dalton M, Bonington A, Hart E, **Gibbons S**, Flegg P, Sweeney J, Wilkins EGL, **Back DJ**. Pharmacological Optimization of PIs and NNRTIs (POPIN)- a randomised controlled trial of therapeutic drug monitoring and adherence support. *J Acquir Immune Defic Syndr* 2006;41(4):461-7. Citations: 43 Impact Factor: 4.653

4. Details of the impact

Those benefiting from the UoL TDM research in the period 2008-2013 are 1) patients and patient groups through optimisation of appropriate treatment doses and therefore better disease prognosis; 2) healthcare providers who are more effectively using their resources; 3) the economy through continued high levels of ritonavir sales and; 4) commerce through the performance of a spin-out company.

Impact on health policy and patient welfare

Although TDM was incorporated into guidelines of many European countries (including the UK) before the current REF evaluation period, TDM was introduced into US national (DHHS) guidelines in 2008. In the UK, around 4,000 TDM tests are requested from >100 NHS Trusts each year. TDM is recommended in selected, often difficult to treat patients, including children, pregnancy, liver impairment, suspected non-adherence and clinical failure.

Examples of guidelines developed since 2008 which recommend use of TDM are British HIV Association Guidelines for HIV treatment in Adults (2012), Pregnancy (2012), TB co-infection

(2011), European Pediatric Treatment (PENTA) guidelines (2009) , European AIDS Clinical Society Treatment Guidelines (2012; translated into 13 languages) [8-12]. The UoL's role in influencing both the policy, and its subsequent implementation includes (i) developing the requisite evidence base through studies describing variability, linking that variability to failure, (ii) being one of the earliest to undertake an RCT to examine the utility of TDM, (iii) developing the infrastructure to deliver a national (and international) TDM service which was comprehensive in number of drugs analysed, quality assured (GCLP) and timely, (iv) developing the training and education required to undertake TDM (talks, written/web resources including webcasts), (v) tools to interpret TDM such as mathematical models, particularly when optimal sampling is difficult e.g. evening dosing, children and (vi) advocacy.

TDM interpretation algorithms were developed in Liverpool from 2008 – 2010, and adopted across the UK, as well as by the HIV TDM reference laboratory in Torino, Italy (currently undertakes 3,500 TDMs/ year). Since 2008, the UoL has developed new TDM assays, including for darunavir, raltegravir, etravirine, rilpivirine and maraviroc - these now account for over a third of TDM requests.

The uptake of TDM across the UK, and widespread adoption into a broad range of BHIVA guidelines attests to the utility of TDM in complex patients and clinical scenarios such as extremes of age and body weight, pregnancy, drug interactions, drug toxicity, poor treatment response or adherence, renal or liver impairment, acute opportunistic infection, solid organ transplantation or malignancy.

Modelling outputs since 2008 have informed health policy, changed clinical practice and drug labelling, e.g. challenging systematic and widespread underdosing of young children and optimising the use of TB and HIV drugs in late pregnancy. Examples include:

- WHO guidelines revising rifampicin/isoniazid pediatric dosing (2010) cited 3 PKPDia studies.
- Malawian Ministry of Health dosing guidelines revised to include pediatric formulations, informed by UoL PK data
- Modelling and simulation of oral dihydroartemisinin-piperaquine in malaria argued for revised dosing for children, now under review by WHO and Medicines for Malaria Venture.
- Modelling and simulation of intramuscular artesunate in severe malaria argued for revised dosing in children, now under review by the manufacturer.
- International (including WHO) guidelines on dosing of lopinavir and efavirenz have been informed by PKPDia studies.

Impact on economy

Use of ritonavir as a 'booster' has expanded globally as a consequence of the UoL's initial description, and is now the standard of care globally. Since 2008, co-formulation of lopinavir/ritonavir has been licensed for children, and generic formulations (manufactured in India and Brazil) are a backbone of second line regimens utilised in low/middle income countries (eg approximately 9% of treated patients across sub-Saharan Africa are on boosted protease inhibitors). New formulations of darunavir (the most commonly prescribed protease inhibitor in the UK) requiring ritonavir boosting were introduced for children (2012) and adults (2013).

Impact on Health & Wealth

Following initial spin-out of TDM from the University in 2005 to Delphic Diagnostics, the company grew as a direct result, adding a further 4 full time positions between 2008-2009. TDM was acquired by Lab21 in Dec 2009, and a new laboratory service introduced in 2010 (with continuing input from the University of Liverpool). In addition, a second laboratory at St George's Hospital, London established TDM for HIV from 2008 onwards. An international quality control programme reported that by the end of 2009, 56 laboratories across the world were offering TDM [16].

5. Sources to corroborate the impact

Each source listed below provides evidence for the corresponding numbered claim made in section 4 (details of the impact).

The following guidelines demonstrate the adoption of TDM into the standard treatments for HIV.

8. British HIV Association guidelines for the treatment of HIV-infected adults with antiretroviral therapy (2012). Gazzard B, on behalf of the BHIVA Writing Committee. *HIV Med*, 9: 563-608.

9. BHIVA treatment guidelines for TB/HIV infection. Pozniak AL, Miller RF, Lipman MCI, Freedman AR, Ormerod LP, Johnson MA, Collins S, Lucas SB, on behalf of the BHIVA guidelines writing committee. (2005). *HIV Med,* 6 (suppl 2): 62-83.

10. BHIVA Guidelines on treatment of HIV in Pregnancy (www.bhiva.org)

11. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (January 29, 2008) Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council

12. European AIDS Clincial Society Guidelines for treatment of HIV infected adults in Europe. (http://www.eacsociety.org/Portals/0/Guidelines_Online_131014.pdf)

The following papers in the scientific literature demonstrate the widespread use of TDM across the developed world, and establishment of laboratory infrastructure to deliver this diagnostic.

13. van Luin M, Kuks PF, Burger DM. Use of therapeutic drug monitoring in HIV disease. Curr Opin HIV AIDS. 2008 May;3(3):266-71.

14. Higgins N, Tseng A, Sheehan NL, la Porte CJ. Antiretroviral therapeutic drug monitoring in Canada: current status and recommendations for clinical practice. Can J Hosp Pharm. 2009 Nov;62(6):500-9.

15. La Porte CJL, **Back DJ**, Blaschke T, Boucher CAB, Fletcher CV, Flexner C, et al. Updated guidelines to perform therapeutic drug monitoring for antiretroviral agents. Rev Antiviral Ther. 2006;3:4–14

16. Burger et al, The International Interlaboratory Quality Control Program for Measurement of Antiretroviral Drugs in Plasma: a global proficiency testing program. Ther Drug Monit 2011;33(2):239-43.