Institution: University College London

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Biological characterisation and impact of HIV drug resistance

1. Summary of the impact

UCL investigators have been at the forefront of characterising and assessing HIV drug resistance since 1990, soon after the very first HIV drug was licenced. There are currently more than 25 drugs available, and our work over the last 23 years has directly determined how best these therapies are used, and monitored in infected patients. We have extended our work to a global perspective, in conjunction with the current rollout of antiretroviral therapy to areas of the world devastated by the epidemic – work which now informs guidelines of the World Health Organisation (WHO), and has resulted in a marked reduction in mortality.

2. Underpinning research

An estimated 35 million people are infected with HIV worldwide, with the vast majority living in the resource poor world. HIV therapy is now provided as a combination of three drugs, in order to prevent drug resistance developing. Our research has been at the forefront of understanding the nature and impact of drug resistance and has therefore shaped all national and international treatment guidelines since the early 1990's.

Our work started with the development of novel gene sequencing and allele-specific methods to show that drug resistance underpinned the lack of treatment effect within the first European pivotal trial of zidovudine monotherapy (Concorde trial) **[1]** and subsequent dual therapy Delta trial **[2]** (**Tedder, Loveday, Weller**). Indeed, this established for the first time the use of genetic markers to directly inform clinical practice. Subsequent rollout of viral gene sequence technology to UK diagnostic laboratories led to the establishment of the UK HIV Drug Resistance Database in 1999, based within UCL (**Pillay)** and the MRC Clinical Trials Unit, now part of UCL (**Dunn, Porter**). The purpose was to map the spread of drug resistance by HIV in the UK, including the transmission of resistance **[3]** (**Pillay, Phillips, Sabin, Geretti**). Indeed, applying new phylogenetic approaches, we have demonstrated a continual spread of drug resistance viruses (**Hue, Kellam**), and their ability to replicate fully, thus requiring new classes of HIV therapy **[4]**. From this base we have extended our national collaboration into a large European dataset, to provide the definitive evidence for the detrimental impact of transmitted drug resistance on outcome of therapy **[5]** (**Pillay, Phillips, Cozzi Lepri, Dunn, Porter**), and thus determine the optimal therapeutic strategies to maximise patient benefit.

During the last 10 years, we have taken this knowledge to map transmission of drug resistance on a global scale. Through describing resistance emerging during the pivotal MRC- funded DART trial of therapy in Africa (**Dunn, Pillay),** and subsequently determining the risks and predictors of such resistance (**Gupta, Cozzi Lepri)**, we highlighted the risk of a large scale transmission of resistance across the resource poor world. Recently, we have indeed demonstrated that such transmission is now a reality, in a paper co-authored with the World Health Organisation **[6]** (**Gupta, Pillay). This commitment to apply our research to the areas of greatest need has led Deenan Pillay to be seconded from UCL to become Director of the Wellcome Trust Africa Centre for Health and Population Sciences, in South Africa- in the highest HIV prevalance area in the world.**

<u>UCL Investigators</u>

Richard Tedder, Senior Lecturer, Reader, then Professor of Virology (1986-)
Clive Loveday, Senior Lecturer then Professor of Virology (1990- 2005)
Ian Weller Professor of HIV Medicine (1987-2010)
Deenan Pillay, Reader, then Professor of Virology (2003-)
Andrew Phillips, Senior Lecturer, Reader, then Professor of Epidemiology (1990-)

Caroline Sabin, Senior Lecturer, Reader then Professor of Medical Statistics (1996-)
Paul Kellam, Senior Lecturer, Reader then Professor of Host Pathogen Research (2000-) (now joint appointment with Wellcome Trust Sanger Institute)
Stephane Hue, Post-Doctoral Research Assistant, then Lecturer in Virology (2006-)
Ravi Gupta, Clinical Research Fellow, then WT Intermediate Clinical Fellow, Senior Lecturer in Infectious Diseases (2007-)
Alessandra Cozzi Lepri, Senior Lecturer in Epidemiology (2005-)
Anna Maria Geretti, Senior Lecturer in Virology (2005-2011)
David Dunn, Senior Lecturer, Reader (2000-)
Kholoud Porter, Senior Lecturer, Reader, Professor (1997-)

3. References to the research

[1] Loveday C, Kaye S, Tenant-Flowers M, Semple M, Ayliffe U, Weller IV, Tedder RS. HIV-1 RNA serum-load and resistant viral genotypes during early zidovudine therapy. Lancet. 1995 Apr 1;345(8953):820-4. http://dx.doi.org/10.1016/S0140-6736(95)92963-0 .

[2] Brun-Vézinet F, Boucher C, Loveday C, Descamps D, Fauveau V, Izopet J, Jeffries D, Kaye S, Krzyanowski C, Nunn A, Schuurman R, Seigneurin JM, Tamalet C, Tedder R, Weber J, Weverling GJ; The National Virology Groups. Delta Virology Working Group and Coordinating Committee. HIV-1 viral load, phenotype, and resistance in a subset of drug-naive participants from the Delta trial. Lancet. 1997 Oct 4;350(9083):983-90. http://dx.doi.org/10.1016/S0140-6736(97)03380-1

[3] Cane P, Chrystie I, Dunn D, Evans B, Geretti AM, Green H, Phillips A, Pillay D, Porter K, Pozniak A, Sabin C, Smit E, Weber J, Zuckerman M; UK Group on Transmitted HIV Drug Resistance. Time trends in primary resistance to HIV drugs in the United Kingdom: multicentre observational study. BMJ. 2005 Dec 10;331(7529):1368. http://dx.doi.org/10.1136/bmj.38665.534595.55

[4] Phillips AN, Leen C, Wilson A, Anderson J, Dunn D, Schwenk A, Orkin C, Hill T, Fisher M, Walsh J, Pillay D, Bansi L, Gazzard B, Easterbrook P, Gilson R, Johnson M, Sabin CA; UK Collaborative HIV Cohort (CHIC) Study. Risk of extensive virological failure to the three original antiretroviral drug classes over long-term follow-up from the start of therapy in patients with HIV infection: an observational cohort study. Lancet. 2007 Dec 8;370(9603):1923-8. http://dx.doi.org/10.1016/S0140-6736(07)61815-7

[5] Wittkop L, Günthard HF, de Wolf F, Dunn D, Cozzi-Lepri A, de Luca A, Kücherer C, Obel N, von Wyl V, Masquelier B, Stephan C, Torti C, Antinori A, García F, Judd A, Porter K, Thiébaut R, Castro H, van Sighem AI, Colin C, Kjaer J, Lundgren JD, Paredes R, Pozniak A, Clotet B, Phillips A, Pillay D*, Chêne G* (* joint senior author); for theEuroCoord-CHAIN study group. Effect of transmitted drug resistance on virological and immunological response to initial combination antiretroviral therapy for HIV (EuroCoord-CHAIN joint project): a European multicohort study. Lancet Infect Dis. 2011 May;11(5):363-71. http://dx.doi.org/10.1016/S1473-3099(11)70032-9

[6] Gupta RK, Jordan MR, Sultan BJ, Hill A, Davis DH, Gregson J, Sawyer AW, Hamers RL, Ndembi N, Pillay D, Bertagnolio S. Global trends in antiretroviral resistance in treatment-naïve individuals with HIV after rollout of antiretroviral treatment in resource-limited settings: a global collaborative study and meta-regression analysis. Lancet. 2012 Oct 6;380(9849):1250-8. http://dx.doi.org/10.1016/S0140-6736(12)61038-1

4. Details of the impact

The underpinning research described above has provided the key evidence base to inform national and international strategy on the treatment of HIV. Our work provided an initial understanding of the molecular basis of drug resistance, and was pivotal to the development and implementation of

sequence-based resistance testing across the NHS, along with the establishment of a national surveillance scheme. With more appropriate first-line therapy, based on individual resistance patterns, the subsequent risk of drug failure due to resistance has been reduced, leading to an overall reduction in resistance. Transmitted drug resistance in the UK has fallen from over 15% of new infections in 2000-2, to fewer than 10% in 2007 and onwards **[a]** representing a reduction of 300 new infections with such resistance per year.

Our work is referenced widely in treatment guidelines around the world. The British HIV Association recommend, based on our evidence of significant levels of transmitted resistance, that drug resistance testing is undertaken BEFORE initiating therapy **[b] Our data represent the first such demonstration in the UK in 2001, leading directly to a change in national guidleines**. The International AIDS Society-USA guidelines also cite our research and named input in support of their recommendations on the mutational definitions of antiretroviral drug resistance **[c]**.

Through a linked biological-epidemiological approach to measuring drug resistance, we have established the national surveillance structure, on behalf of Public health England. In 2011, we provided evidence to the House of Lords Select Committee on HIV and AIDS, the report from which stated; "*It is essential, though, that treatment does not cause longer-term harm. If a person fails to stick to a regime of antiretroviral drugs, it can lead to the development of drug resistance, as has been seen with antibiotics. Were such resistance to become widespread, treatment efforts would be hampered in the long-term. This is closely monitored. The United Kingdom has the largest resistance database linked to clinical data in the world, to ensure that any problems are quickly identified. With no vaccine and no cure, it is important that surveillance systems robustly monitor and contain the risk of emerging antiretroviral resistance (see paras 227 to 228)*" **[d]**.

In 2012, UCL led a major Seminar on the "Impact of HIV drug resistance in the resource poor world" in conjunction with the WHO in Geneva, 2012 **[e]**. This was the first such meeting to include both generic and proprietary drug producers, to establish the future of rational drug treatment for the developing world. As a consequence, in 2013, the World Health Organisation (WHO) changed its surveillance strategy to better guide appropriate interventions in the developing world. Based on our findings from the UK population, WHO established a monitoring function, in parallel with the rollout of antiretroviral therapy **[f]**. As one of five such specialist Laboratories worldwide, we supported this monitoring. In light of our recent finding of an increase in transmitted drug resistance in Eastern Africa, the WHO has altered their surveillance approach towards a more feasible and cost-effective approach of those individuals starting therapy. We are currently in the vanguard of a major policy change within the WHO regarding recommendations for first and second line therapies for the developing world. This will affect 35 million infected individuals, with the likely impact being the introduction of viral quantification monitoring to guide switch from first to second line therapy. This is evidenced through a joint publication with WHO (e) and reference to our work in the 2013 revised WHO Guidelines **[Chapter 7 ref 165 g]**.

5. Sources to corroborate the impact

[a] UK Collaborative Group on HIV Drug Resistance, Dolling D, Sabin C, Delpech V, Smit E, Pozniak A, Asboe D, Brown AL, Churchill D, Williams I, Geretti AM, Phillips A, Mackie N, Murphy G, Castro H, Pillay D, Cane P, Dunn D, Dolling D. Time trends in drug resistant HIV-1 infections in the United Kingdom up to 2009: multicentre observational study. BMJ. 2012 Aug 21;345:e5253. http://dx.doi.org/10.1136/bmj.e5253.

[b] British HIV Association Treatment Guidelines. First edition, and all subsequent updates. http://www.bhiva.org/documents/Guidelines/Treatment%20Guidelines/Archive/2003/Treatment%20Guidelines%202003.pdf.

[c] International AIDS Society-USA HIV Treatment Guidelines 2012. https://www.iasusa.org/content/antiretroviral-treatment-adult-hiv-infection-0

[d] No Vaccine, no cure: HIV and AIDS in the United Kingdom. Select Committee on HIV and

AIDS in the United Kingdom.
http://www.publications.parliament.uk/pa/ld201012/ldselect/ldaids/188/18802.htm

[e] Bertagnolio S, Perno CF, Vella S, Pillay D. The Impact of HIV Drug Resistance on the Selection of First- and Second-Line ART in Resource-Limited Settings. J Infect Dis. 2013 Jun 15;207 Suppl 2 http://jid.oxfordjournals.org/content/207/suppl_2.toc

[f] WHO HIV Drug Resistance Report 2012. http://www.who.int/hiv/pub/drugresistance/report2012/en/index.html. References the worldwide importance of UCL based work in guiding WHO surveillance schemes

[g] Consolidated Guidelines on The use of antiretroviral drugs for treating and preventing HIV Infection. World Health Organisation, June 2013 http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf