Institution: The University of Edinburgh

Unit of Assessment: UoA5 Biological Sciences

Title of case study:
Mutations in the HIV genome are used to combat drug resistance, for tracking infection, and in litigation.

Period when the underpinning research was undertaken: 2000-2018

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Prof Andrew Leigh-Brown	Professor of Evolutionary Genetics	1984-present

Period when the claimed impact occurred: 2013-2020

Is this case study continued from a case study submitted in 2014? Y/N No

1. Summary of the impact

Attribution: Research at the University of Edinburgh into genetic mutations and transmission patterns in HIV have improved patient treatment, drug development, and contact tracing, which is now called upon during court cases in Scotland, England and Wales.

Impact on health and well-being: Sets of HIV mutations identified by Leigh Brown are included in the Stanford HIV Drug Resistance Data base, plus an UK-equivalent database. These are used by clinicians treating patients with HIV, by public health officials monitoring HIV drug resistance, and also by pharmaceutical companies developing new drugs to fight HIV.

Impact on public policy and services: Informed by Leigh-Brown's research, Public Health England and the U.S. Centre for Disease Control (CDC) now use HIV sequence data to track transmission in populations, and it is a cornerstone of "Ending the Epidemic – A Plan for America".

Impact on Law: Corroboration of HIV transmission by phylogenetic analysis is deemed essential in England & Wales and Scotland court cases according to Guidelines for prosecutors.

Beneficiaries: people at risk of and living with HIV, clinicians, Public Health bodies in UK and USA, HIV charities and lobby groups, criminal justice systems.

Significance and Reach: Identification of genetic mutations in HIV has improved drug delivery for patients and enabled targeted drug development by pharmaceutical companies. Genetic contact tracing has also allowed the identification of hidden at risk groups, the importance of which was highlighted in the 2019 State of the Union address (USA). This impact has had local (Scotland), national (England and Wales) and international (Ireland and USA) reach.

2. Underpinning research

HIV is genetically diverse within infected individuals and between populations globally. Leigh Brown's research has played a key role in characterising this viral diversity, using his expertise in population genetics and evolutionary biology to identify and track the spread of mutations that inform medical practice and societal applications.

Mutations associated with drug resistance. HIV mutations confer resistance to antiretroviral drugs if drugs are delivered individually. The pathways to resistance can be simple (one mutation in the active site), or complex and variable (involving numerous mutations, *e.g.* at protease inhibitors). Leigh Brown's group at Edinburgh applied statistical and machine learning approaches to identify previously unrecognised complex patterns of mutations conferring resistance [3.1,3.2], with a direct relevance to patient treatment that was recognised by their inclusion in databases and published lists of mutations for clinical recommendations (Europe, UK and USA).

Disease spread from hidden risk groups. Starting in 2006, the group began to use the UK HIV Drug Resistance Database (UKHIVRDB) of HIV sequences to reveal patterns of HIV transmission within the UK using phylogenetics and network theory. Recently, this work revealed a distinct risk group, not identifiable from routine surveillance data, of men declaring their risk as heterosexual rather than homosexual contact, but whose infection was found to link only to men [3.3]. This work pioneered rapid methods for detecting linked infections in very large databases [3.4,3.5], and promoted focused health information messaging [3.6]. The importance of using phylogenetic analysis and these methods for such purposes was explicitly recognised in the US President's "Ending the HIV Epidemic: A Plan for America" (State of the Union Address 2019).

HIV and the Law. The first case of HIV transmission to be the subject of a criminal prosecution in the UK (R v Kelly) involved subjects recruited in 1993 to an MRC-funded research project led by ALB and published in 1997. The prosecution reached court in 2001 and was followed by several prosecutions in England. Phylogenetic analysis of HIV sequences were included in the Kelly case but not initially in England. In 2014, the Crown Prosecution Service then produced guidelines requiring it in all cases.

3. References to the research

[3.1] R. J. Murray, F. I. Lewis, M. D. Miller, A. J. Leigh Brown, Genetic basis of variation in tenofovir drug susceptibility in HIV-1. AIDS. 22, 1113–1123 (2008). https://doi.org/10.1097/QAD.0b013e32830184a1

[3.2] H. M. Precious, H. F. Gunthard, J. K. Wong, R. T. D'Aquila, V. A. Johnson, D. R. Kuritzkes, D. D. Richman, A. J. Leigh Brown, Multiple sites in HIV-1 reverse transcriptase associated with virological response to combination therapy. AIDS. 14, 31–36 (2000) https://doi.org/10.1097/00002030-200001070-00004

[3.3] M. Ragonnet-Cronin, S. Hue, E. B. Hodcroft, A. Tostevin, D. Dunn, T. Fawcett, A. Pozniak, A. E. Brown, V. Delpech, A. J. Leigh Brown, Non-disclosed men who have sex with men in UK HIV transmission networks: phylogenetic analysis of surveillance data. Lancet HIV. 5, e309–e316 (2018) https://doi.org/10.1016/S2352-3018(18)30062-6

[3.4] Wertheim JO, Leigh Brown AJ, Hepler NL, et al. The Global transmission network of HIV-1. J Infect Dis 2013 Oct 22;209:304-13. https://doi.org/10.1093/infdis/jit524

[3.5] Kosakovsky Pond SL, Weaver S, Leigh Brown AJ, Wertheim JO. HIV-TRACE (Transmission Cluster Engine): a tool for large scale molecular epidemiology of HIV-1 and other rapidly evolving pathogens. Mol Biol Evol 2018 Jan 31;35:1812-9. https://doi.org/10.1093/molbev/msy016

[3.6] L. Mulka, J. H. Vera, A. J. Leigh-Brown, J. A. Cassell, How can we use phylogenetics to facilitate clinical case finding and partner notification in hiv: lessons from a systematic review of its use in stigmatised infectious diseases. Sex Transm Infect. 93, A141 (2017) http://dx.doi.org/10.1136/sextrans-2017-053264.364

4. Details of the impact

Work lead by Leigh-Brown on the genetic diversity and spread of HIV has directly impacted health, policy and the law.

Impact on health and well-being:

Sets of HIV mutations identified by the Leigh Brown's group at Edinburgh were included in the Stanford HIV Drug Resistance Data base [5.1] and the UKHIV drug resistance database [5.2]. These are considered by clinicians to tailor the appropriate drug treatment for the individual, by public health officials monitoring HIV drug resistance, and also by pharmaceutical companies developing new drugs to fight HIV. This is important because, although anti-retroviral drugs are effective, HIV mutates at a high rate and can develop drug resistance. In people receiving treatment, this can lead to treatment failure, disease progression, and transmission to other untreated individuals. Leigh Brown also sits on the steering committee of the UK HIV Drug Resistance Database.

Impact on public policy and services:

Public Health England and the U.S. Centre for Disease Control (CDC) use HIV sequence data to track transmission in populations, and it and the methods developed [3.5] form a cornerstone of "Ending the Epidemic – A Plan for America" [5.3].

Policy changes by the CDC and Public Health England

The US Centre for Disease Control (CDC) released the first version of "Detecting and Responding to HIV Transmission Clusters - A Guide for Health Departments" in 2016/17. This was updated in June 2018 [5.4]. Leigh Brown's research describing the use of HIV-TRACE (TRAnsmission Cluster Engine Tool) is referenced in this document (Appendix G), and is referred to in a letter of support from the CDC's Deputy Associate Director of Science [5.5]. The use of HIV sequence data to analyse characteristics of HIV transmission have now also been adopted by Public Health England (PHE), as referred to in a letter of support from PHE's head of national HIV surveillance [5.6]. Specifically, the UKHIV Drug Resistance Database [5.2] is referenced in both the 2016 and 2017 PHE HIV annual reports [5.7i & ii], with Leigh Brown's publication being referenced in the 2017 report. The 2017 report looks at the potential for the elimination of HIV transmission, AIDS and HIV-related deaths in the UK. This is a recent and welcome change [5.8]. Services to monitor transmission events, HIV transmitted drug resistance, the role of accessory mutations in levels of HIV drug resistance are some of the genome sequencing services offered by the Antiviral Unit, PHE.

State of the Union Address 2019

The power of HIV sequence analysis for tracking transmission, as shown by Leigh Brown's work identifying hidden risk groups, has been explicitly recognised in "Ending the HIV Epidemic: A Plan for America". This plan was highlighted in the State of the Union Address 2019 [5.3] as a critical tool for identifying accelerating outbreaks and guiding intervention.

Impact on Law:

Corroboration of HIV transmission by phylogenetic analysis is deemed essential in England, Wales and Scotland court cases according to Guidelines for prosecutors. Specifically, for cases where transmission has occurred, an expert will be required to give evidence that phylogenetic analysis of samples of the victim and accused produced a result consistent with transmission between the two individuals concerned. Therefore, identification of the accused as the source of the infection in cases of transmission must be corroborated.

England and Wales – The Crown Prosecution Service of England & Wales released Legal guidance on Intentional or Reckless Sexual Transmission of Infection in 2013 (outwith the REF impact period but in practice *throughout* the period [current CPS guidelines 5.9]. Leigh Brown's phylogenetic research is referenced in a section of the guidelines which addresses the use of phylogenetic evidence where a defendant is accused of reckless transmission of the virus [5.10i]. The international campaign group HIV Justice Network (https://www.hivjustice.net [5.10ii]) lists over 25 criminal cases in the UK involving HIV transmission from 2014-present. In one of these, a case in Coventry in 2015, the lack of phylogenetic evidence was specifically identified as a reason for a charge to be dropped [5.10iii].

Scotland - Crown Office and Procurator Fiscal Service (COPFS) guidance for prosecutors on the "Intentional or reckless sexual transmission of, or exposure to, infection". These guidelines for prosecutors, produced in July 2014, state that it is essential to provide evidence showing that the victim contracted the infection from the accused [5.11]. The guidelines were drafted in conjunction with the National Aids Trust.

Leigh Brown's body of research using phylogenetic analysis to show transmission patterns is the underlying research that this impact relies upon and the first prosecution of HIV transmission in the UK involved two individuals who had been recruited to, and had their virus sequenced in a research study he led. Subsequently he appeared as an expert witness in this case. He has in addition acted as expert witness in court cases in the UK and wider (Republic of Ireland [5.12] during REF period).

In 2018, Leigh Brown was called upon by the legal team acting for the defence in an Irish criminal case to discuss the significance of phylogenetic scientific evidence with the court. The Republic of Ireland was unusual in not routinely using phylogenetic evidence as a matter of course, as indeed it is now standard practice (England and Wales, and Scotland) for scientific evidence to be included in court proceedings: cases may be, and have been, dismissed by the judge where this evidence has been omitted. Scottish guidelines stipulate that scientific evidence is essential to *support* a case but cannot on its own convict.

5. Sources to corroborate the impact

[5.1] Stanford HIV drug resistance database: https://hivdb.stanford.edu/

[5.2] UK HIV drug resistance database: http://www.hivrdb.org.uk/

[5.3] 2019 US State of the Union address: https://www.hiv.gov/federal-response/ending-the-hiv-epidemic/overview.

[5.4] CDC Guidance on Detecting and Responding to HIV Transmission Clusters: Appendix G. Additional resources (note that this document remains stamped 'draft', we have CDC confirmation that this is the up-to-date version): https://www.cdc.gov/hiv/pdf/funding/announcements/ps18-1802/CDC-HIV-PS18-1802-AttachmentE-Detecting-Investigating-and-Responding-to-HIV-Transmission-Clusters.pdf

[5.5] CDC - Deputy Associate Director for Science - letter of support.

[5.6] Public Health England - Consultant epidemiologist & head of national HIV surveillance; letter of support.

[5.7] i) HIV in the UK: 2016 report, Appendix 7: p44

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/602942/HIV_in_the_UK_report.pdf

ii) Towards elimination of HIV transmission, AIDS and HIV-related deaths in the UK: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/675809/Towards_elimination_of_HIV_transmission_AIDS_and_HIV_related_deaths_in_the_UK.pdf "Recent trends and patterns in HIV-1 transmitted drug resistance in the United Kingdom", https://doi.org/10.1111/hiv.12414 Cited on pg36.

[5.8] AntiViral Unit Reference Services: https://www.gov.uk/guidance/antiviral-unit-avu-reference-services

[5.9] Intentional or Reckless Sexual Transmission of Infection – Crown Prosecution Service England & Wales Legal guidance: https://www.cps.gov.uk/legal-guidance/intentional-or-reckless-sexual-transmission-infection

[5.10] i) HIV Transmission, the Law and the Work of the Clinical Team, January 2013. Phillips M, Poulton M, on behalf of the British HIV Association (BHIVA) and British Association of Sexual Health and HIV (BASHH) writing committee. Pg 6, Pg24, ref 18 http://www.hepatitisscotland.org.uk/files/2813/6076/6404/5267186-HIV-Transmission-the-Law-and-the-Work-of-the-Clinical-Team-January-2013-Matthew-Phillips-Mary-Poulton-on-behalf-of-the-British-HIV-Association-BH.pdf
ii) The international campaign group HIV Justice Network: https://www.hivjustice.net
iii) Reckless HIV transmission case dropped due to lack of phylogenetic report: https://www.hivjustice.net/cases/uk-cps-drops-reckless-hiv-transmission-prosecution-due-to-lack-of-phylogenetic-report/

[5.11] Crown Office and Procurator Fiscal Service (COPFS) guidance for prosecutors - INTENTIONAL OR RECKLESS SEXUAL TRANSMISSION OF, OR EXPOSURE TO, INFECTION (Use of Experts in HIV cases) https://www.copfs.gov.uk/images/Documents/Prosecution_Policy_Guidance/Guidelines_and_Policy/Prosecution%20policy%20on%20the%20sexual%20transmission%20of%20infection%20-%20July%2014.pdf

[5.12] Irish Times Story on Intentional Transmission of HIV: daily circulation 79,021 as of 2019: https://www.irishtimes.com/news/crime-and-law/courts/circuit-court/man-found-guilty-of-intentionally-infecting-women-with-hiv-1.3562868