Institution: The University of Oxford

Unit of Assessment: 1

Title of case study:

IMPROVING HIV TREATMENT

Summary of the impact:
Highly Active Anti-Retroviral Therapy (HAART) is a combination of drugs used to effectively control HIV infection. Since 1987 Nucleoside Reverse Transcriptase Inhibitors (NRTIs) had been used in HAART combinations to specifically target HIV-1 reverse transcriptase, however, resistance and side effects soon prompted the need for an alternative. In 1998, University of Oxford Professors David Stuart and David Stammers provided the first detailed structural framework to facilitate the design of a highly effective alternative class of drug, the Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs). NNRTIs have since been developed for clinical use, impacting the pharmaceutical industry and profoundly improving the quality of life of patients.

Underpinning research:
For HIV to replicate, it must first convert its RNA genome into DNA. This is achieved by the reverse transcriptase (RT) enzyme, which is encoded by the HIV genome. The resulting DNA serves as a template for the creation of more HIV RNA genomes, which can then be assembled into new viral offspring. Reverse transcription is particularly vulnerable to errors. Over many generations of viral replication, this leads to high genetic diversity, which can in turn lead to drug resistance.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs) were the first antiretroviral drugs developed to control AIDS, but because NRTIs were used as monotherapy, HIV soon developed resistance to the drug. Plagued by resistance and a number of unpleasant side effects, including fat deposition and nausea, the need for an alternative therapy quickly became a priority for HIV researchers. Discovered serendipitously in 1989, Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) were extremely susceptible to resistance via single amino acid changes in HIV-1 RT. The mechanism of NNRTI action and the nature of its interactions with the target, however, remained unknown. After the crystal structure of HIV-1 RT was published in 1992[1], work by the University of Oxford's David Stuart refined this model by producing a series of papers in 1995 describing the first high-resolution structures of NNRTIs and HIV-RT and other data, which became the basis for structure-based drug design[2-5]. The structure of RT-NNRTI complexes identified structural features, which correlated with potency, providing an explanation for the mode of action of these compounds[3].

In 1996 Professor David Stammers joined Professor Stuart and his team at the University of Oxford. Professor Stammers' spin off company, Arrow Therapeutics, assisted the group in delving further into the development of NNRTI drug therapy. They then shared this information with GlaxoWellcome Pharmaceuticals (now GlaxoSmithKline). The Oxford group provided a database of atomic information to GlaxoWellcome, prior to the intellectual property becoming public domain, enabling the early development of NNRTI drug therapy. This atomic information still comprises over 50% of the available data on NNRTIs, while collaborative studies involving the University of Oxford's structural biologists have also provided detailed explanations for the mechanisms leading to drug resistance[4,5]. Continuing this collaboration with industry, specific chemical series were devised which were outstandingly refractory to the development of resistance[6], one of which (GW695634) entered phase II clinical trials in 2005. The GW695634 chemical series generated the prodrug (a compound modified for active use in the body) of GW678248, an NNRTI with potent antiviral activity against efavirenz- and nevirapine-resistant HIV-1 viruses. This has led to the development of a second-generation of NNRTIs for use in HAART drug combinations.

References to the research:

1. Kohlstaedt, L. A., Wang, J., Friedman, J. M., Rice, P. A. & Steitz, T. A. Crystal structure at 3.5 A resolution of HIV-1 reverse transcriptase complexed with an inhibitor. *Science* **256**, 1783–1790 (1992) doi:10.1126/science.1377403. ***This paper reports the first crystal***

structure of HIV-1 RT heterodimer at 3.5 A complexed with the NNRTI nevirapine, revealing features relating to the mechanism of NNRTI inhibition.

2. Ren, J. *et al.* High resolution structures of HIV-1 RT from four RT-inhibitor complexes. *Nat. Struct. Biol.* **2**, 293–302 (1995). ***This was the first report from Oxford providing structural information of four HIV-RT and NNRTI complexes useful for drug design.***

3. Esnouf, R. *et al.* Mechanism of inhibition of HIV-1 reverse transcriptase by non-nucleoside inhibitors. *Nat. Struct. Biol.* **2**, 303–308 (1995). ***The 2.35 A structure of the unliganded HIV-1 RT from the Oxford group defined the conformational changes required to form the NNRTI binding site on RT. This elucidates a common mechanism of inhibition by a diverse class of HIV-1 RT inhibitors.***

4. Ren, J. *et al.* The structure of HIV-1 reverse transcriptase complexed with 9-chloro-TIBO: lessons for inhibitor design. *Structure* **3**, 915–926 (1995). ***This study by the Oxford group suggests structural constraints on the repertoire of mutations that can escape inhibition without compromising virus viability.***

5. Ren, J. *et al.* Structural mechanisms of drug resistance for mutations at codons 181 and 188 in HIV-1 reverse transcriptase and the improved resilience of second generation non-nucleoside inhibitors. *J. Mol. Biol.* **312**, 795–805 (2001). ***The crystal structures reported from the Oxford group revealed details of resistance mechanisms that could be used to formulate general rules for drug design of novel inhibitors of HIV-1 RT.***

6. Hopkins, A. L. *et al.* Complexes of HIV-1 reverse transcriptase with inhibitors of the HEPT series reveal conformational changes relevant to the design of potent non-nucleoside inhibitors. *J. Med. Chem.* **39**, 1589–1600 (1996). doi: 10.1021/jm960056x
This paper reports the structures of HIV-1 RT with inhibitors of the same class. Details on their binding suggested a strategy for designing inhibitors that require more than one RT mutation to diminish inhibitor efficacy.

This research was funded by the Medical Research Council's AIDS Directed Programme, with Glaxo Wellcome.

Details of the impact:

Research undertaken by the Structural Biology Group at the University of Oxford has not only had a broad impact on the programmes of several pharmaceutical companies, and the quality of life of those living with HIV, it also continues to inform efforts aimed at the development of improved anti-HIV compounds[7].

Commercialisation:

The GW695634 chemical series, which became the prodrug for GW678248 has led to the production of a powerful NNRTI active against efavirenz- and nevirapine-resistant HIV-1 viruses. Following phase II trials undertaken by GlaxoWellcome in 2005, this NNRTI has since been licensed to a number of pharmaceutical companies around the world for drug development. Most NNRTIs approved for the clinic from 2000 onwards were optimised based on the Stuart Groups structure-based design. These include etravirine, which was developed by Johnson & Johnson, and rilpiravine a second generation NNRTI with an improved therapeutic index, both of which are produced by Tibotec Pharmaceuticals[8]. Pfizer, the largest pharmaceutical company in the world, replicated the protein constructs and crystallization methods from the University of Oxford's Stuart Group, using similar structural information to conceive new drug targets. As a result Pfizer produced X-ray protein structures of all of their key anti-HIV compounds, several of which (including Lersivirine, formally known as UK-453,061) advanced into clinical trials, but were never licensed for therapy[9]. ViiV Healthcare, a specialist HIV pharmaceutical company driven by GlaxoSmithKline and Pfizer, is now developing Lersivirine in Phase III trials. There are currently 2 more NNRTIs in late-stage development; Ardea BioScience's RDEA806 and ViiV's GSK-2248761. In addition, global pharmaceutical companies such as Gilead[10] and Merck[11] have all used data

from the Stuart Group in their NNRTI drug development pipelines. At present there are 5 NNRTIs licensed for clinical use. The anti-HIV drug sales market stood at $11.3billion in 2010 and this is projected to rise yearly by 4.6% (The Global Market for AIDS/HIV testing and Treatment – BCC Research 2011). Globally, there is an increase in the use of HAART, which is reflected in these figures.

Patient Health & Quality of Life

A recent epidemiological study, evaluating current issues in the management of HIV-infected patients, found that the availability of potent next-generation NNRTIs might offer improved therapy for treatment-experienced patients, particularly those with multi-resistant HIV. The study also showed that new NNRTI drugs may reduce HIV immunological and clinical progression, and as a result, may also reduce treatment costs[12]. Median survival time after infection with HIV without treatment is 11 years, contrasting with survival time close to 50 years for an HIV-infected individual treated from age 20 (UNAIDS Reference Group for Estimates, Modeling and Projections, 2006). After AIDS diagnosis however, untreated individuals survive to 6-19 months post diagnosis whereas with treatment many individuals recover to a stable latent state of infection with survival rates of ~50 years, approximating other HIV-infected individuals (Antiretroviral Therapy Cohort Collaboration report, Lancet, 372:293-299, 2008). In a study analysing the cost-effectiveness of first line HAART regimens in UK patient groups over the period 1996-2006, it was shown that a regimen of 2NRTIs + NNRTI was the most effective therapy. In comparison to the alternative regimen of 2NRTIs + PI (boosted) the study showed that the + NNRTI regimen saved £35,194 per annum in HAART treatments[13]. Effective HAART therapy can now be shown to achieve survival rates for people living with HIV equivalent to those in the general population[14], emphasizing the success of new generation ART drug regimens.

Policy and Guidelines

Clinical guidelines worldwide now recommend NNRTIs in combination with NRTIs as the first line therapy for HIV. The standard HAART combination of two NRTIs with an NNRTI, is recommended by the World Health Organization in their guidelines for antiretroviral therapy for HIV infection in adults and adolescents (last revised in 2010)[15]. The British HIV Association guidelines for the treatment of HIV-infected adults with antiretroviral therapy recommend the use of an efavirenz-based regimen as the first line choice for patients with HIV[16]. They based this recommendation on data, which has indicated the efficacy, low toxicity and the ease of administration of efavirenz NNRTIs, which were developed based on the Stuart Groups structure-based design.

Sources to corroborate the impact:

7. Ren, J. et al. Structural basis for the improved drug resistance profile of new generation benzophenone non-nucleoside HIV-1 reverse transcriptase inhibitors. J. Med. Chem. 51, 5000–5008 (2008) doi: 10.1021/jm8004493
This paper provides a proof of principle for drug design based on the structural features of benzophenone inhibitor binding to HIV-1.

8. Das, K. et al. Roles of conformational and positional adaptability in structure-based design of TMC125-R165335 (etravirine) and related non-nucleoside reverse transcriptase inhibitors that are highly potent and effective against wild-type and drug-resistant HIV-1 variants. J. Med. Chem. 47, 2550–2560 (2004) doi: 10.1021/jm030558s ***This paper cites the elasticity of the NNRTI binding site, resistance mutations Tyr 181 and Tyr188 and the structure data from Oxford of HIV-1 RT in complex with many inhibitors as key drug design features for novel RT inhibitors.***

9. Pfizer A Phase 2B Multicenter, Randomized, Comparative Trial Of UK-453,061 Versus Etravirine In Combination With Darunavir/Ritonavir And A Nucleos(t)Ide Reverse Transcriptase Inhibitor For The Treatment Of Antiretroviral Experienced HIV-1 Infected Subjects With Evidence Of NNRTI Resistant HIV-1 - Full Text View In: ClinicalTrials.gov Bethesda (MD) National Library of Medicine (US) 2000- (Accessed 2013) Available at http://clinicaltrials.gov/show/NCT00823979 NLM Identifier: NCT00823979

This 96 week clinical study (reported August 2012) compares the efficacy of lersivirine (UK-453,061) vs etravirine. Although the drugs were not ultimately licensed for the clinic, the method of structure-based design (developed by the Stuart group) is key to the development of these new drugs.

10. Lansdon, E. B. et al. Crystal structures of HIV-1 reverse transcriptase with etravirine (TMC125) and rilpivirine (TMC278): implications for drug design. J. Med. Chem. 53, 4295–4299 (2010) doi: 10.1021/jm1002233.
This study recognises the flexible properties in some NNRTI structures and the allosteric mechanism of inhibition in the choice of pipeline drug targets.

11. Gomez, R. et al. Design and synthesis of pyridone inhibitors of non-nucleoside reverse transcriptase. Bioorg. Med. Chem. Lett. 21, 7344–7350 (2011) doi: 10.1016/j.bmcl.2011.10.027.
This paper from Merck describes the design and structural characterisation of the pyridone class of NNRTIs. The drug design rationale utilised a combination of elements derived from the Oxford work.

12. Boyd, M. A. & Hill, A. M. Clinical management of treatment-experienced, HIV/AIDS patients in the combination antiretroviral therapy era. Pharmacoeconomics 28 Suppl 1, 17–34 (2010) doi: 10.2165/11587420-000000000-00000.
This paper reports the improved efficacy of HAART that includes next-generation components (PIs, NNRTIs, integrase and entry-inhibitors) particularly for patients with existing resistance mutations.

13. Beck, E. J. et al. Cost-effectiveness of early treatment with first-line NNRTI-based HAART regimens in the UK, 1996-2006. PLoS ONE 6, e20200 (2011) doi: 10.1371/journal.pone.0020200.
This retrospective study of 7600 people living with HIV in the UK analysed the clinical and health economic benefits of 2NRTI + NNRTI therapy vs 2NRTI + PI therapy for first-, second- or third-line treatment.

14. Obel, N. et al. Impact of non-HIV and HIV risk factors on survival in HIV-infected patients on HAART: a population-based nationwide cohort study. PLoS ONE 6, e22698 (2011) doi: 10.1371/journal.pone.0022698.
This recent study shows that for people living with HIV with no other risk factors, effective HAART therapy leads to a mortality rate equivalent to that of the general population with no risk factors.

15. WHO HIV/AIDS Programme. Antiretroviral therapy for HIV infection in adults and adolescents - recommendations for a public health approach. (Accessed 2013). Available at http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf ***These WHO HIV/AIDS Programme guidelines 2010 recommend efavirenz or nevirapine as NNRTIs to be added to first-line regimens for adults and adolescents, with 2 NRTIs + NNRTI as the preferential approach.***

16. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012. Doi 10.1111/j.1468-1293.2012.01029_1.x. Accessed at http://www.bhiva.org/documents/Guidelines/Treatment/2012/hiv1029_2.pdf
Guidelines recommending the use of an efavirenz-based regimen as the first line choice for patients with HIV16. This recommendation was based on data developed using the Stuart Group's structure-based design.