Institution: Imperial College London

Unit of Assessment: 01 Clinical Medicine

Title of case study: Preventing the progression of latent TB in HIV patients.

Period when the underpinning research was undertaken: 2005 - 2014

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:
Robert John Wilkinson	Professor of Infectious Diseases	2004 – present
Hanif Esmail	Wellcome Fellow	2010 - 2013

Period when the claimed impact occurred: 2014 - present

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

1. Summary of the impact (indicative maximum 100 words)

25% of the global population harbour latent tuberculosis infection (LTBI); HIV-1 infection greatly increases the risk of activation of LTBI, leading to overt lung disease. The team at Imperial College led an intervention in South Africa which reduced the reactivation of LBTI by 37%, through adding concurrent prophylactic Isoniazid to anti-retroviral HIV therapy (ART). This led to new guidelines for the management of HIV in UK and South Africa, subsequently adopted by WHO in its recommendation for isoniazid to be prescribed with initiation of ART in high-risk environments. This simple, effective intervention has now been widely adopted by PEPfAR in Sub-Saharan Africa.

2. Underpinning research (indicative maximum 500 words)

HIV-associated tuberculosis has a mortality rate that can exceed 20% and is the commonest cause of AIDS death in Sub-Saharan Africa. The prevention of tuberculosis (TB) in HIV-infected people is therefore a priority, and indeed crucial to achieve the Sustainable Development Goal 3.3 to end the epidemics of TB and AIDS. Prof Robert Wilkinson led a research group in Cape Town South Africa for 17 years, focussed on the immunological interactions of HIV-1 and TB and the clinical consequences, including the diagnosis of latent TB infection (1, 2).

Work from Prof Wilkinson's team and that of many others established that HIV antiretroviral therapy (ART) reduces the individual risk of TB by 50-80%. South Africa has particularly high rates of TB. In 2004 the annual notification rate in parts of peri-urban Cape Town was 1,612 per 100,000 overall, rising to >10,000 per 100,000 (i.e. 10%) per annum among HIV-1 infected people. An initial plan for the control of TB in Cape Town, based on the WHO case-finding strategy, was not controlling this TB/HIV epidemic, creating an urgent need to find new public health measures to prevent the re-activation of latent TB infection (LTBI) caused by HIV co-infection.

This underpinning research provided the impetus to assess isoniazid (antitubercular) preventive therapy (IPT) on the development of overt TB disease in HIV-infected people concurrently initiating ART, by means of a randomized clinical trial. The intervention comprised 1,329 HIV-1 infected subjects in Cape Town, South Africa who were randomly allocated to receive ART plus either IPT or a placebo for 12 months, with a total of 3,227 person-years of follow up (3). The primary endpoint was time to develop overt TB disease. 95 incident cases of TB were identified during follow-up; 37 were in the isoniazid preventive therapy group, at a

rate of 2·3 per 100 person-years (95% confidence interval 1·6–3·1); 58 TB cases were in the placebo group, at a rate of 3·6 per 100 person-years (hazard ratio 0·63, 95% confidence interval 0·41–0·94). These results illustrated a 37% reduction in the development of overt TB cases in the ART plus concurrent isoniazid arm compared to ART alone. The efficacy was observed irrespective of evidence of immune sensitization (by interferon-gamma release assay).

The study concluded that IPT should be recommended to all HIV-infected people receiving ART in moderate or high prevalence areas for latent TB infection, irrespective of tuberculin skin test or interferon gamma release assay status (4). Modelling the research findings predicted that combining ART with concurrent IPT lowers overt TB disease incidence by 23% among people receiving ART, and by 5.2% in the total population. By adopting this intervention, one TB death would be averted for every 158 HIV-infected individuals treated (5,6).

3. References to the research (indicative maximum of six references)

(1) Rangaka, M.X., Wilkinson, K.A., Seldon, R., van Cutsem, G., Meintjes, G.A., Morroni, C., Mouton, P., Diwakar, L., Connell, T.G., Maartens, G., and Wilkinson, R.J. (2007). The Effect of HIV-1 infection on T cell based and skin test detection of tuberculosis infection. *American Journal of Respiratory and Critical Care Medicine*;175(5): 514-520. DOI.

(2) Esmail, H., Lai R., P-J., Lesosky, M., Wilkinson, K.A., Graham, C.M., Coussens, A.K., Oni, T., Warwick, J.M., Said-Hartley, Q., Koegelenberg, C.F., Walzl, G., Flynn, J.L., Young, D.B., Barry 3rd, C.E., O'Garra, A., Wilkinson, R.J. (2016). Characterization of progressive HIV-associated tuberculosis using 2-deoxy-2-[18F]fluoro-D-glucose positron emission and computed tomography. *Nature Medicine*; 22(10):1090-1093. DOI.

(3) Rangaka, M.X., Wilkinson, R.J., Boulle, A., Glynn, J.R., Fielding, K., van Cutsem, G., Goliath, R., Mathee, S., Goemaere, E., Maartens, G. (2014). Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind placebo-controlled trial**.** *Lancet*; 384(9944):682-90. DOI.

(4) Getahun, H., Matteelli, A., Abubakar, I., Aziz, M.A., Baddeley, A., Barreira, D., Den Boon, S., Gutierrez, S.M.B., Bruchfeld, J., Burhan, E., Cavalcante, S., Cedillos, R., Chaisson, R., … Wilkinson, R.J., Yoshiyama, T., Zellweger, J.P., Raviglione, M. (2015). Management of latent *Mycobacterium tuberculosis* infection: WHO guidelines for low tuberculosis burden countries. *European Respiratory Journal*; 46(6):1563-76. DOI

(5) Sumner, T., Houben, R., Rangaka, M.X., Maartens, G., Boulle, A., Wilkinson, R.J., White, R. (2016). Modelling the post-treatment effect of isoniazid plus antiretroviral therapy on tuberculosis incidence. *AIDS*; 30(8):1279-86. DOI

(6) Kendall, E.A., Azman, A.S., Maartens, G., Boulle, A., Wilkinson, R.J., *et al.* (2019). Projected population-wide impact of antiretroviral therapy-linked isoniazid preventive therapy in a high-burden setting. AIDS; 33: 525-536. DOI

Grants supporting the work:
i) Three Wellcome Trust Senior Fellowships in Clinical Science to Wilkinson
Understanding tuberculosis in Cape Town, South Africa
October 2004-September 2009, reference 072070/Z/03/Z, £1,126,305
Triple intervention against tuberculosis
WT088316 October 2009-September 2014, £1,477,974
Host directed therapies against tuberculosis
WT104803MA October 2014-September 2020 £2,857,319
ii) Wellcome Trust Strategic award
Clinical infectious diseases research initiative at the University of Cape Town

WT084323MA, June 2008-December 2013, £3,270,000
iii) Wellcome Trust Centres competition
Centre for Infectious Diseases Research in Africa (CIDRI-Africa)
203135/Z/16/Z 7th March 2017-6th March 2022, £5,416,590

4. Details of the impact (indicative maximum 750 words)

The prevention of overt TB in latently infected subjects through use of prophylactic isoniazid was widely recognised prior to the HIV epidemic. However, the findings of the research led by Prof Wilkinson demonstrated for the first time in a randomised trial that concurrent ART plus IPT could be safely and effectively combined to reduce the reactivation of latent TB in HIV-infected subjects, leading to a 37% reduction in overt TB disease. Previous reports of the use of IPT in HIV infection to prevent LTBI had been small and observational only, without randomisation. The independent TEMPRANO randomised trial subsequently confirmed Wilkinson's teams' result, reporting a 35% reduced risk of death in a similar population intervention [**A**].

In the Western Cape of South Africa, a peak TB incidence of 1,024 per 100,000 in 2006, fell substantially (by 39%) to 625 per 100,000 by 2015; this reduction occurred almost exclusively in HIV-infected persons. Whilst overall TB incidence in South Africa peaked in 2010-11, it still remains exceptionally high. It is difficult to disentangle the multiple interventions which led to this reduction in TB incidence and especially the contribution of ART alone; however, the research work by Prof Wilkinson was widely disseminated in the Western Cape from 2012 onwards, was a substantial and novel catalyst in this achievement and underpinned the change to national and international treatment guidelines.

Changes to international guidelines as a result of this research:

The provision of at least 9 months of IPT to HIV-infected persons receiving ART in high TB incidence areas has become a policy guideline worldwide as a result of the research findings at Imperial College plus those generated from contemporary and subsequent randomised studies by colleagues. These guidelines include:

• The South African HIV Society ART guidelines for adults in 2017 recommend that all patients receiving ART should be considered for IPT [**C**, see page 22]

• The British HIV Association (BHIVA) guidelines for the management of TB/HIV co-infection in 2019 recommends testing for, and treatment of, LTBI with IPT for all HIV-positive individuals who are close contacts of people with infectious TB [**D**]

• The WHO guidelines were updated in 2018 and recommend: "*Adults and adolescents living with HIV, with unknown or a positive tuberculin skin test (TST) and are unlikely to have active TB should receive preventive treatment of TB as part of a comprehensive package of HIV care. Treatment should be given to these individuals irrespective of the degree of immunosuppression and also to those on antiretroviral treatment (ART), those who have previously been treated for TB and pregnant women. (Strong recommendation, high-quality evidence)"* [**E**].

The underpinning work by the Imperial researchers has been specifically highlighted by leaders in the field of TB as particularly important work [**F**] and included as advice in recent US NCA and CDC guidelines [**G**]. The research has been incorporated to a single-stage meta-analysis of isoniazid prophylaxis using individual participant data through stratified Cox-proportional hazards models [**H**]. This analysis concluded that IPT, concurrent with ART, prevents overt TB disease across demographic and HIV-specific and TB-specific subgroups, aligning with current guidelines and thus supporting efforts to further increase use of IPT plus ART broadly among people living with HIV.

Roll-out of IPT beyond South Africa:

ART plus IPT is now being scaled up widely in and beyond South Africa; in 2016, the US President's Emergency Plan for AIDS Relief (PEPfAR) Scientific Advisory Board recommended the promotion of concurrent IPT with ART [**B**]; subsequently in 2019, PEPfAR committed to targets of 14,600,000 people living with HIV and AIDS and in care and taking ART also receiving concurrent IPT. PEPfAR has now led successful scale up elsewhere in sub-Saharan Africa most notably in Kenya, Uganda and Nigeria – a direct consequence of the evidence underpinning the WHO guidelines [**E**], to which Wilkinson's research contributed significantly.

Largely in recognition of this work Wilkinson was awarded the International Union against Tuberculosis and Lung Disease *Scientific prize* in 2020 [**I**].

5. Sources to corroborate the impact (indicative maximum of 10 references)

[**A**] TEMPRANO ANRS Danel C, Moh R, Gabillard D, Badje A, *et al*. (2015). A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *N Engl J Med*;373(9):808-22. DOI

[**B**] PEPfAR Scientific Advisory Board. https://www.state.gov/wp-content/uploads/2020/08/2016-SAB-Recommendations-to-Prevent-and-Treat-TB-among-PLHIV.pdf (Archived here).

[**C**] South African HIV Society ART guidelines for adults http://www.sahivsoc.org/Files/Adult_ART_2017.pdf (Archived here).

[**D**] British HIV association guidelines for the management of TB/HIV co-infection in adults updated 2019 https://doi.org/10.1111/hiv.12748 and https://www.bhiva.org/file/wciyxvzCuTmjD/BHIVA-TB-HIV-co-infection-guidelines-consultation.pdf (archived here).

[**E**] WHO Guidelines for the treatment of latent tuberculosis – 2018. https://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/ (archived here)

[**F**] Harries A: F1000Prime Recommendation of [Rangaka MX et al., Lancet 2014]. In F1000Prime, 08 Sep 2014; https://f1000.com/prime/718391872

[**G**] Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020 Morbidity and Mortality Weekly Report February 14 2020 https://www.cdc.gov/mmwr/volumes/69/rr/pdfs/rr6901a1-H.pdf (Archived here).

[**H**] Ross, J.M., Badje, A., Rangaka, M.X., Walker, S., Shapiro, A.E., Thomas, K.K. Anglaret, X., Eholie, S., Gabillard, D., Boulle, A., Maartens, G., Wilkinson, R.J., Ford, N., Golub, J.E., Williams, B.G., Barnabas, R.V. Isoniazid Preventive Therapy Added to ART to Prevent TB: An Individual Participant Data Meta-Analysis *Lancet HIV* (2021) 8: e8–15 DOI

[**I**] https://theunion.org/news/the-union's-2020-annual-awards-recognise-significant-contributions-to-lung-health (Archived here).