Institution: London School of Hygiene & Tropical Medicine (LSHTM)

Unit of Assessment: UoA2 – Public Health, Health Services & Primary Care

Title of case study: Isoniazid preventive therapy for people with HIV

1. Summary of the impact

LSHTM research has resulted in isoniazid preventive therapy (IPT) becoming one of the key interventions recommended by WHO to reduce the impact of tuberculosis (TB) among HIV-positive people. As a direct result of the research findings, WHO recommendations now promote wider use of IPT. In addition, barriers to implementation have been overcome, leading to increasing worldwide use of IPT for TB prevention among people with HIV. A companion case study addresses impact on screening for TB amongst such people.

2. Underpinning research

TB is a major cause of death among HIV-positive people. In the pre-HIV era, IPT was an important intervention for preventing TB, but its efficacy among people with HIV was unknown. This has been the focus of work for researchers at LSHTM including Professors of International Health Alison Grant (LSHTM since 1994, MRC Training Fellow 1994-7), John Porter (LSHTM since 1990, then Senior Clinical Lecturer) and Peter Godfrey-Faussett (LSHTM since 1989, then Clinical Research Fellow).

Between 1992 and 1998, Porter led randomised trials to determine the efficacy of isoniazid in preventing TB among HIV-positive adults in Kenya (N=684) and Zambia (N=1053), the latter with Godfrey-Faussett.[3.1] The results of the Kenyan trial were inconclusive, but the Zambian trial demonstrated that preventive therapy with twice-weekly isoniazid for six months reduced the incidence of TB among people with HIV.

Based on these findings, Godfrey-Faussett, currently on secondment to WHO, led the development of new WHO guidelines on IPT use. With WHO support, Godfrey-Faussett undertook pioneering research between 1999 and 2004, integrating TB and HIV care at primary care level, featuring IPT as a key intervention.

Starting in 1999, Grant undertook a series of studies addressing obstacles to IPT implementation, collaborating with South African researchers, in the setting of the intense TB epidemic in South African gold mines. An observational cohort study demonstrated effectiveness of IPT among people with HIV and a past history of TB (for whom IPT was not previously recommended in WHO guidelines).[3.2] Using an innovative study design, 1,655 HIV-positive male employees of a South African gold-mining company were offered enrolment in HIV care, in a randomly-allocated sequence. Key findings were that enrolment in a clinic offering IPT (300mg daily for six months, self-administered) to these gold miners reduced TB incidence by 38% overall, and by 46% among individuals with no prior history of TB, although post-IPT TB incidence in this setting remained unacceptably high.[3.3]

Further work led by Grant included a meta-analysis showing that the risk of developing isoniazid resistance after IPT was small.[3.4] Qualitative work in South Africa identified that health care worker perceptions were a major barriers to IPT use. In 2010 Grant was commissioned by WHO to produce a systematic review of TB/HIV integration which directly informed updated WHO guidelines on TB/HIV collaborative activities.[3.5]

In the 'Thibela TB' trial (2004-12) Grant, with colleagues in South Africa, led a cluster-randomised study of community-wide IPT among gold miners in South Africa, as a population-level strategy to control the TB epidemic. This study enrolled 24,221 miners to start IPT – the largest number of people ever to receive IPT in a clinical trial. Prior to enrolment, nurses used clinical criteria to screen participants for active TB and increased risk of isoniazid toxicity using a questionnaire and chest radiograph. Study-defined IPT-related adverse events were checked at each study visit. Key findings were that adverse events were extremely rare, and IPT could be safely implemented by

nurses using clinical criteria.[3.6] The main study results are currently in press.

3. References to the research

3.1 Mwinga, A, Hosp, M, Godfrey-Faussett, P, Quigley, M, Mwaba, P, Mugala, BN, Nyirenda, O, Luo, N, Pobee, J, Elliott, AM, McAdam, KPWJ and Porter, JDH (1998) Twice weekly tuberculosis preventive therapy in HIV infection in Zambia, *AIDS*, 12(18): 2447–2457, doi: 10.1097/00002030-199818000-00014. Citation count: 158.

3.2 Churchyard, GJ, Fielding, K, Charalambous, S, Day, JH, Corbett, EL, Hayes, RJ, Chaisson, RE, De Cock, KM, Samb, B and Grant, AD (2003) Efficacy of secondary isoniazid preventive therapy among HIV-infected Southern Africans: time to change policy? *AIDS*, 17(14): 2063–2070, http://journals.lww.com/aidsonline/Fulltext/2003/09260/Efficacy_of_secondary_isoniazid_preventive_therapy.7.aspx (accessed 14th November 2013). Citation count: 59.

3.3 Grant, AD, Charalambous, S, Fielding, KL, Day, JH, Corbett, EL, Chaisson, RE, De Cock, KM, Hayes, RJ and Churchyard, GJ (2005) Effect of routine isoniazid preventive therapy on tuberculosis incidence among HIV-infected men in South Africa: a novel randomized incremental recruitment study, *JAMA-Journal of the American Medical Association*, 293(22): 2719–2725, doi: 10.1001/jama.293.22.2719. Citation count: 69.

3.4 Balcells, ME, Thomas, SL, Godfrey-Faussett, P and Grant, AD (2006) Isoniazid preventive therapy and risk for resistant tuberculosis, *Emerging Infectious Diseases*, 12(5): 744–7451, http://wwwnc.cdc.gov/eid/article/12/5/pdfs/05-0681.pdf (accessed 14 November 2013). Citation count: 70.

3.5 Legido-Quigley, H, Montgomery, CM, Khan, P, Atun, R, Fakoya, A, Getahun, H and Grant, AD (2013) Integrating tuberculosis and HIV services in low- and middle-income countries: a systematic review, *Tropical Medicine & International Health*, 18(2): 199–211, doi: 10.1111/tmi.12029. Citation count: 0

3.6 Grant, AD, Mngadi, KT, van Halsema, CL, Luttig, MM, Fielding, KL and Churchyard, GJ (2010) Adverse events with isoniazid preventive therapy: experience from a large trial, *AIDS*, 24(Suppl. 5): s29–36, doi: 10.1097/01.aids.0000391019.10661.66. Citation count: 7.

Key grants

Award to Aurum Institute, South Africa, co-PI Grant, Effect of Community-wide Isoniazid Preventive Therapy on Tuberculosis Among South African Gold Miners, Bill and Melinda Gates Foundation, 2004–2013, US$27m.
Grant, National Public Health Career Scientist Award, UK Department of Health, 2003–2008, £688,000 (portfolio including work on Thibela TB).
Godfrey-Faussett, Innovations Programme, The Zambian ProTEST Project, Department for International Development, 1999–2001, £192,900.
Porter, Prevention of HIV-related TB in Zambia, WHO, 1992–1997, $521,000.
Porter, Prevention of HIV-related TB in Zambia, 1992–1997, Overseas Development Association, £447,000.
Porter, Prevention of HIV-related TB in Kenya, MRC, 1990–1994. £250,000.

4. Details of the impact

Work by LSHTM researchers into TB prevention among people with HIV has directly informed the evolution of WHO guidelines on IPT since 1998, including the most recent update in 2011, and updated guidance on TB and HIV collaborative activities in 2012. It has also provided evidence for key stakeholders to adopt IPT.

Drawing directly on Porter's Kenyan and Zambian trials, IPT became one of the key interventions recommended by WHO in 1998[5.1] to reduce the burden of TB in people living with HIV – yet implementation of IPT was initially very slow. In 2005 only 25,000 people living with HIV worldwide were reported to have received it.

A series of research articles about IPT, including Grant and Godfrey-Faussett as co-authors, was published in 2010 in *AIDS*,[5.2, 5.3] the International AIDS Society's official journal, made publicly available, open access, via their website to 16,000 members from 196 countries including clinicians, public health and community practitioners, policy and programme planners. The same edition also contains an opinion piece that heavily draws on LSHTM research.[5.4]

At the AIDS 2012 Conference in Washington, Grant was invited to present her research regarding new approaches for TB prevention.[5.5] This was reported, among others, by *HIV & AIDS Treatment in Practice*, a widely read email newsletter distributed to practitioners worldwide.[5.6]

As part of Grant's 'Thibela TB' trial (ended 2012), over 24,000 miners started IPT, the largest number in any clinical trial. Beyond the health benefit experienced by those participating in the trial, the results, in combination with Grant's data from the meta-analyses about drug resistance after IPT, and on how to screen for active TB prior to IPT, were directly fed into the revision of WHO guidelines on IPT. In 2010 Grant and Godfrey-Faussett were invited to join the WHO Guidelines Group, reviewing new scientific evidence and contributing LSHTM research into the process which led to a revision of WHO guidelines.[5.7] As a direct result of LSHTM research, new recommendations included that isoniazid should be offered to individuals regardless of previous tuberculosis history,[3.2] and that people living with HIV should be screened for active TB using a tool derived largely from LSHTM research. The guidelines also draw directly on the LSHTM research in addressing the misconceptions that may contribute to the low uptake of isoniazid therapy – for example the concern that using isoniazid without other TB medications promotes drug resistance.

The following year (2011) Godfrey-Faussett was a member of WHO's policy updating group, responsible for advising WHO concerning collaborative TB/HIV activities in response to demand from countries for guidance on actions to decrease the dual burden of TB and HIV. Drawing on LSHTM research,[3.5] the updated policy emphasised the need to establish mechanisms for integrated TB and HIV services, preferably at the same time and location.[5.8]

Grant's Thibela TB research has been particularly influential in promoting IPT use in South Africa. Through work with key collaborators such as the Aurum Institute, greater stakeholder and political awareness of the efficacy of IPT was raised. In 2009, the South African Minister of Health said of the Thibela TB study: 'your research on the community-wide use of isoniazid has that ground-breaking feel'.[5.9] In his opening speech at the South African AIDS Conference (Durban, June 2013), the Minister of Health, Dr Aaron Motsoaledi, referred directly to LSHTM research when he said: 'This decline [in TB deaths] has been attributed by researchers to the increased number of HIV positive patients on ARVs as well as the screening for TB and putting eligible patients on IPT … This is very good news!'[5.10]

5. Sources to corroborate the impact

5.1 WHO, Global Tuberculosis Programme, UNAIDS (1998) *Policy Statement on Preventive Therapy Against Tuberculosis in People Living with HIV: Report of a Meeting Held in Geneva 18–20 February 1998*, WHO/TB/98.255; UNAIDS/98.34. Geneva: WHO, http://whqlibdoc.who.int/hq/1998/WHO_TB_98.255.pdf (accessed 14 November 2013).

5.2 Eldred, LJ, Churchyard, G, Durovni, B, Godfrey-Faussett, P, Grant, AD, Getahun, H and Chaisson, RE (2010) Isoniazid preventive therapy for HIV-infected people: evidence to support implementation, *AIDS*, 24(Suppl. 5): s1–3, doi: 10.1097/01.aids.0000391009.95149.ec.

5.3 Chaisson, RE, Grant, A, Getahun, H and Glynn, JR (eds) (2010) Implementation of isoniazid preventive therapy to control HIV-related tuberculosis: evidence, challenges and policy, *AIDS*, 24(Suppl. 5), http://journals.lww.com/aidsonline/toc/2010/11005 (accessed 14 November 2013) (supplement of the journal AIDS devoted to IPT).

5.4 Getahun, H, Granich, R, Sculier, D, Gunneberg, C, Blanc, L, Nunn, P and Raviglione, M

(2010) Implementation of isoniazid preventive therapy for people living with HIV worldwide: barriers and solutions, *AIDS*, 24(Suppl. 5): s57–65, http://journals.lww.com/aidsonline/Fulltext/2010/11005/Implementation_of_isoniazid_preventive_therapy_for.9.aspx (accessed 14 November 2013).

5.5 XIX International AIDS Conference 22–27 July, Washington DC
Grant, A (2012) TB prevention: new data, new approaches, new challenges, paper presented at the XIX International AIDS Conference, 22–27 July, Washington DC, http://pag.aids2012.org/session.aspx?s=651 (accessed 14 November 2013).
Stop TB Partnership (2012) Whoopi Goldberg calls for action on childhood TB at International AIDS Conference, press release, 27 July. Geneva: WHO, http://www.stoptb.org/news/stories/2012/ns12_049.asp (accessed 14 November 2013) (includes reference to Grant).

5.6 TB and HIV news from the 19th International AIDS Conference (2012) *HATiP: HIV & AIDS Treatment in Practice*, 198: 5–11, http://www.aidsmap.com/pdf/HATIP-198-August-6th-2012/page/2468298/ (accessed 14 November 2013).

5.7 WHO (2011) *Guidelines for Intensified Tuberculosis Case-finding and Isoniazid Preventive Therapy for People Living with HIV in Resource-constrained Settings*. Geneva: WHO, http://whqlibdoc.who.int/publications/2011/9789241500708_eng.pdf (accessed 14 November 2013) (2011 guidelines on IPT: multiple items of LSHTM research are cited, particularly references 5, 15 – LSHTM provided most of the data and multiple staff are authors – 27, 38, 39 – Grant's work – 42, 43 – trials mentioned in this case study).

5.8 WHO (2012) *WHO policy on Collaborative TV/HIV Activities: Guidelines for National Programmes and Other Stakeholders*. Geneva: WHO, http://www.who.int/tb/publications/2012/tb_hiv_policy_9789241503006/en/ (accessed 14 November 2013) (updated policy on TB HIV collaborative activities, which draws directly on 3.4 and 3.5).

5.9 The Aurum Institute *A Prospectus for Victory*. Johannesburg: The Aurum Institute, https://sitefinder.tghn.org/site_media/media/site_finder/sites/documents/Aurum_Prospectus.pdf (accessed 14 November 2013) (p. 7).

5.10 Motsoaledi, A (2013) Opening speech by the Minister of Health, delivered at the South African AIDS Conference, 18 June, Durban, transcript, http://www.doh.gov.za/show.php?id=4305 (accessed 14 November 2013) (refers to LSHTM work on the effect of IPT on mortality).