Institution: University of Bristol

Unit of Assessment: UoA2

Title of case study: Improving treatment guidelines, life expectancy and access to life insurance for HIV positive people

1. Summary of the impact

In 2011, 34 million people worldwide were living with, and 1.7 million died from, HIV/AIDS. Since 2002, HIV-positive people have benefited from research by the Antiretroviral Therapy Cohort Collaboration (ART-CC) based at University of Bristol (UoB). Research on the timing of ART led to updated international HIV treatment guidelines that recommended starting treatment earlier. Research on life expectancy highlighted the benefits to patients of earlier ART, and was used by policy makers, clinicians and patient groups to promote earlier treatment. Patients are now starting treatment earlier resulting in increased life expectancy. Insurance companies changed their criteria for providing life insurance, influenced by ART-CC.

2. Underpinning research

2.1 The Antiretroviral Therapy (ART) Cohort Collaboration

ART-CC is a large collaboration set up in 2000 to study the survival of HIV positive individuals starting treatment with ART. Funded by four successive grants from the Medical Research Council, it includes nineteen cohorts from Europe and North America and is coordinated by a team based in the SSCM, UoB, led by Professor Jonathan Sterne and Dr Margaret May.

2.2 Informing treatment strategies

Analyses published in *The Lancet* in 2002, based on over 12000 patients, identified that the most important predictor of mortality was the CD4 count, a measure of immune deficiency, at which patients started ART [1]. Estimates of cumulative mortality for 80 risk groups were made available via a web-based calculator (www.art-cohort-collaboration.org). Scale-up of treatment in low-income countries started in 2002, and in 2006 ART-CC published the first comparison of mortality of patients starting ART between low and high-income countries [2]. When patients and physicians consider starting ART, they must balance its beneficial effects in preventing AIDS and death with harmful side-effects and the inconvenience of taking lifelong medication. Before 2009 the CD4 count at which ART should be started was a central, unresolved issue in the care of HIV positive people. ART-CC provided evidence that 350 cells/mm^3 should be the minimum CD4 count below which ART should be started [3].

2.3 Life expectancy and the consequences of late treatment

ART-CC found that improvements in treatment for HIV decreased mortality by nearly 40% and increased life expectancy by 13 years in high-income countries between 1996-2005 [4], but that starting treatment too late resulted in poorer survival [1,4]. May worked with the UK Collaborative HIV Cohort (UK CHIC) Study to raise awareness amongst the general public that starting treatment later than guidelines recommended resulted in up to 15 years' loss of life [5]. For patients treated in the UK between 1996 and 2008, life expectancy was 13 years less than that of the UK general population, and lower the later in the course of HIV disease that patients started treatment. Life expectancy at age 20 was 38 years in those who started ART with CD4 count <100, but >53 years in those who started with CD4 between 200 and 350 cells/mm^3.

2.4 Insurability of people living with HIV

In 2009, access to life insurance was very limited for people living with HIV. Swiss Re (a reinsurance company based in Zurich, Switzerland) collaborated with ART-CC to analyse data in the manner most useful for promoting insurance by estimating excess mortality in HIV positive people compared with expected mortality in the insured populations in 6 European countries based on actuarial tables. This research showed that up to 50% of HIV patients in lower risk groups could be eligible for life insurance with terms up to 25 years [6].

ART-CC Co-ordinating Centre, University of Bristol team members

Prof Matthias Egger (2000–4 (Visiting Prof from 2004)); Prof Jonathan Sterne (2000-present); Dr Margaret May (2000-present); Ross Harris (2004-8); Dr Suzanne Ingle (2010-present).

3. References to the research

[1] **Egger M, May M**, **Sterne JAC**. et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. The Lancet. 2002 Jul;360 (9327):119 – 129. doi:10.1016/S0140-6736(02)09411-4

[2] Braitstein, P, et al (including **May, Sterne, Egger**). Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: Comparison between low-income and high-income countries. Lancet, 2006. 367 (9513): p. 817-24. PMID: 16530575 doi:10.1016/S0140-6736(06)68337-2

[3] **Sterne JA, May M**, Costagliola D, **Egger M** et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. Lancet. 2009; 373 (9672): 1352-1363. PMID: 19361855 doi:10.1016/S0140-6736(09)60612-7

[4] ART-CC (including **May, Sterne**). Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet. 2008; 372 (9635): 293-299. PMID: 18657708 doi:10.1016/S0140-6736(08)61113-7

[5] **May M,** Gompels M, Delpech V et al. Impact of late diagnosis and treatment on life expectancy in people with HIV-1: UK Collaborative HIV Cohort (UK CHIC) Study. BMJ 2011, 343:d6016 doi: http://dx.doi.org/10.1136/bmj.d6016

[6] Kaulich-Bartz J, Dam W, **May MT**, Lederberger B et al. **Sterne JAC**.Insurability of HIV-positive people treated with antiretroviral therapy in Europe: collaborative analysis of HIV cohort studies. AIDS 2013; 27:1641-1655 PMID: 3678894 doi: 10.1097/QAD.0b013e3283601199

Medical Research Council (MRC) Peer Reviewed Grants

Sterne JAC (PI), Ingle SM, May M, Egger M, et al. Prognosis of HIV-positive patients treated with antiretroviral therapy: comparative analyses and treatment strategies. MR/J002380/1 £589,409 2012-15.

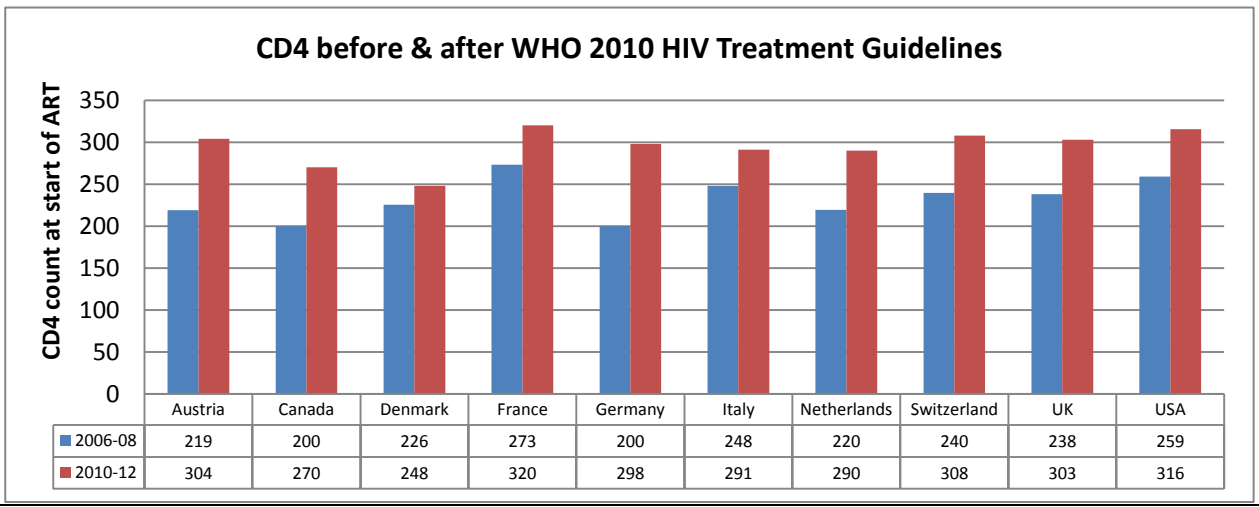
Sterne JAC (PI), May M, Egger M. et al. Monitoring and modelling prognosis in the era of HAART. G0100221 £171,227, 2005-8 and G0700820 £627,188 2008-11.

Egger M (PI), Sterne JAC, et al. The impact of highly active antiretroviral therapy: Monitoring and modelling benefit and potential harm. G0100221, £218,046, 2002-5.

4. Details of the impact

4.1 Updated treatment guidelines resulted in earlier treatment

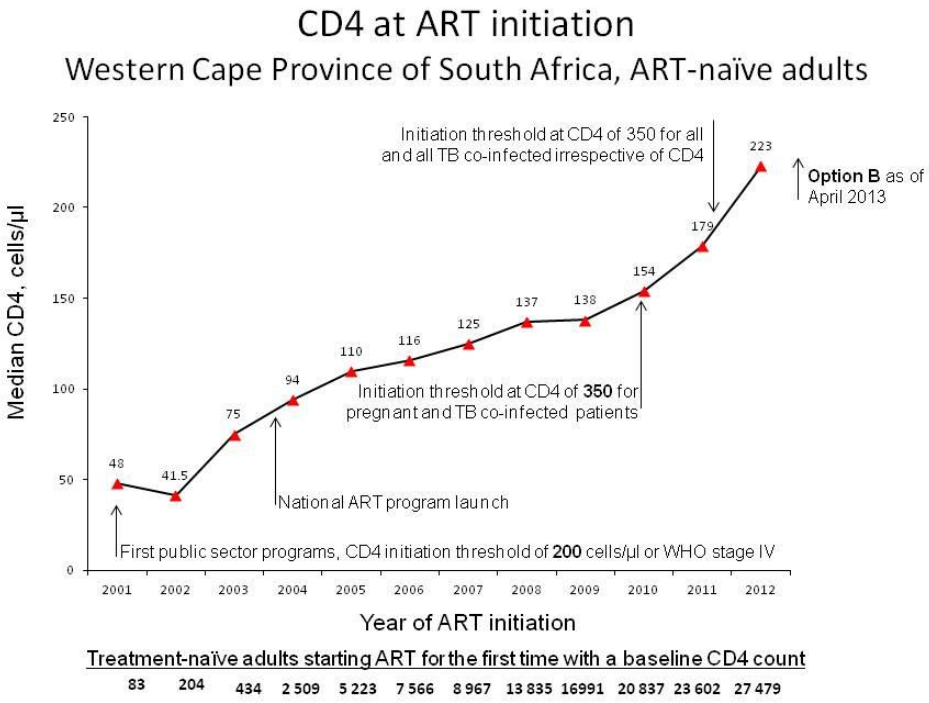
Earlier ART leads to better treatment outcomes for people with HIV throughout the world with fewer deaths and hospitalisations. ART-CC's research on prognosis [1-3] has been extensively cited by treatment guidelines between 2008 and 2013. Our 2009 paper on timing of ART [3], which clarified that the CD4 threshold for starting ART should be at least 350 cells/mm^3, was particularly influential and informed changes during 2009-11 to World Health Organization (WHO) [a], British [b], European, US [c], and other national [d] guidelines to recommend starting treatment earlier.



	Austria	Canada	Denmark	France	Germany	Italy	Netherlands	Switzerland	UK	USA
2006-08	219	200	226	273	200	248	220	240	238	259
2010-12	304	270	248	320	298	291	290	308	303	316

High income countries: ART-CC research suggests that increasing the CD4 count at start of ART from 200 to 350 cells/mm^3 will increase life expectancy of a 20-year-old by between 8 [6] and 12 years [5]. The bar chart on page 2 (based on unpublished ART-CC data) shows that patients started treatment earlier in the UK, Europe and North America after guidelines were changed in 2009-10. The Health Protection Agency (HPA) 2012 report stated that between 2010 and 2011 AIDS diagnoses in the UK decreased by 33% and mortality by 18% [e].

Low income countries: UNAIDS reported that the number of people in Africa receiving ART increased from less than a million in 2005 to 7.1 million in 2012, with nearly 1 million added in 2012 alone. During 2009-11 the recommended threshold for treatment in at least 29 low and middle income countries changed (based in part on ART-CC's work) from 200 to 350 cells/mm^3 [d]. This has led to more and earlier treatment, particularly in Africa. Data from Western Cape, South Africa, show the steep increase in numbers of people treated and their increased CD4 count at start of ART as a consequence of the adoption of the new guidelines (graph - personal communication, Cape Town University, South Africa). During this period, AIDS-related deaths in Africa fell by 32% from approximately 1.75 to 1.19 million (calculated from UNAIDS 2012 global report). The massive scale-up in treatment due to increasing the threshold from 200 to 350 cells/mm^3 has been replicated across the globe.



4.3 Raised public awareness of consequences of starting treatment late

May worked with the UK Collaborative HIV Cohort (UK CHIC) Study to raise awareness of the loss in life expectancy due to starting HIV treatment later than guidelines recommend [6]. This work was extensively reported in the UK and worldwide, for example in a two-page feature in *The Independent* in October 2011 [f] and in *The China Daily* [f] and was also discussed by professional publications such as *Nursing Times*, on 8 November 2011 [f]. The same research was presented in a poster [f] displayed in hospital waiting rooms across the UK, to communicate the findings to patients as part of a wider effort by UKCHIC to disseminate information to key patient communities. According to the 2012 HPA UK HIV report, the proportion of HIV positive people diagnosed late (with CD4 count below 350 cells/mm^3) fell by 3% during 2011 [e].

The ART-CC paper on life expectancy [4] influenced a campaign to halve the proportion of people diagnosed late with HIV [g]. The UK CHIC life expectancy paper [5] contributed evidence to "Standard 1: HIV Testing and Diagnosis" in the policy document from BHIVA on "Standards of Care for People Living with HIV" [h]. Earlier diagnosis and prompt treatment reduces onward transmission since successfully treated people with suppressed virus replication do not transmit

HIV [h]. This not only avoids illnesses and early deaths, but also has the potential to deliver huge financial savings. The HPA 2011 report estimated that the prevention of one new HIV infection saves the public purse between £280,000 and £360,000 in direct lifetime healthcare costs [e]. This research therefore impacts not only the 22,600 people the HPA estimated were living with undiagnosed HIV in the UK in 2011 (2012 report) [e] but also uninfected individuals, who are less likely to be exposed to HIV if those infected with HIV are diagnosed and treated [e].

4.4 Improved access to insurance.

The opportunity to obtain life insurance has a major impact on quality of life, particularly since a term of 20 years is required for a mortgage. ART-CC research [1,6] had a commercial impact by providing data to insurance companies that led them to improve the provision of life insurance and open up the insurance market to HIV positive people. Swiss Re [i], Hannover Re (UK) and AERAS (France) [i] based their assessment of insurability of HIV positive people on ART-CC's publications [1,6] and web-based mortality risk calculator. Based on our 2002 data [1], SwissRe recommended that certain patient groups should be offered up to 10 years' insurance. During 2010-12, ART-CC worked with SwissRe to extend this to 20 years and estimate the excess premium that HIV positive individuals would need to pay [6]. This had an impact prior to publication: ART-CC tables were presented at a national meeting of insurers in Paris [i], and New York [i] by Swiss Re, and to the French AIDS research agency (Agence Nationale de Recherche sur la Sida et les hepatites virales, ANRS) by May[i]. Based on this research, Swiss Re updated its underwriting guidelines for western Europe resulting in cheaper insurance costs and broader coverage with policies offered up to 25 years [j]. The Head of Research Innovation and Product Development, Swiss Re, stated that there would be "greater access to home ownership and to business loans for HIV positive persons" and the research "has led to increased normalisation of HIV compared to other chronic diseases... The study has also influenced Swiss Re's ratings for HIV+ lives in South Africa and the ratings of direct insurers" and "has influenced debate on HIV ratings in India and Australia" [j].

ART-CC research on insurability [6] has impacted awareness of insurance products among HIV positive people through the work of advocacy groups such as HIV i-base [i] and the European AIDS Treatment Group, which in discussing our paper [6] wrote "People doing well on HIV therapy should be eligible for life insurance" [i]. The proportion of UK insurers that provide services to HIV positive people increased from 33% to 66% between 2010 and 2012 [i]. A 2012 UK survey found that the percentage of HIV positive people who knew of the existence of life insurance products increased from only 20% in 2012 to 78% in 2013 [i].

5. Sources to corroborate the impact

[a-d] corroborate influence of ART-CC research on changes in treatment guidelines worldwide, [e-g] on earlier treatment, decreased AIDS and deaths in UK, and [i-j] document increased provision of insurance based on ART-CC analyses.

[a] WHO ART for HIV infection in adults and adolescents: recommendations for a public health approach 2010 revision [cites 2 P65 & 3 P26] http://www.who.int/hiv/pub/arv/adult2010/en/index.html

[b] British HIV Association guidelines for the treatment of HIV-1-positive adults with ART 2012 [cites 3 P22 and 5 P8] http://www.bhiva.org/documents/Guidelines/Treatment/2012/hiv1029_2.pdf

[c] US 2011: Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. 1/2011; 1–166. [cites 1 P7 & extensively discusses 3 P28-9], revision 10/2011 [cites 4 P25] http://aidsinfo.nih.gov/guidelines

[d] Table of low and middle income countries that have changed guidelines to start ART at CD4 count threshold of 350 derived from http://www.aidstar-one.com/

[e] HPA: HIV in the United Kingdom: 2011 [cites 5 P4] and 2012 Annual Reports http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317131685847 and C/1317137200016

[f] Media, NHS and charities awareness reports after publication of paper on life expectancy [5].

[g] Early testing saves lives: HIV is a public health priority. 2nd edition Halve It Coalition. http://www.bhiva.org/documents/Publications/Halve_it_Position_Paper.pdf [cites 4 P7]

[h] BHIVA Standards of Care for People Living with HIV in 2013 – Standard 1: HIV Testing and Diagnosis [cites 5 P12] http://www.bhiva.org/standards-of-care-2012.aspx

[i] PDF Evidence of impact of ART-CC on insurability and awareness of life insurance for HIV+.

[j] Personal statement: Director, Swiss Re.