Institution: University College London

Unit of Assessment: 2 - Public Health, Health Services and Primary Care

Title of case study: Influencing global policy on antiretroviral treatment priorities

1. Summary of the impact

Our work with the World Health Organisation (WHO) had a major impact on global HIV treatment priorities at a critical time in the roll-out of anti-retroviral treatment (ART) worldwide. Concern had been expressed that if ART was provided without simultaneous monitoring of HIV viral load to determine switch in treatment, this would lead to an epidemic of drug resistant HIV. It was argued that viral load monitoring should be introduced as a priority, despite the fact that this was expensive and would inevitably divert resources from ART provision. We used a simulation model to predict the impact of lack of viral load monitoring and showed that while development of viral load assays was important, ART should be prioritised. As a result, the roll out of ART continued despite continued lack of viral load monitoring, and there are now over 9 million people on ART.

2. Underpinning research

The underpinning research described below was carried out by the HIV Epidemiology and Biostatistics Group at UCL led by Professor Andrew Phillips, and was a collaboration with the WHO HIV/AIDS Department.

In the early-2000s, global plans were being put in place to expand access to ART as rapidly as possible to low resource settings (particularly sub-Saharan Africa) where most people with HIV live. In order to make this feasible, the WHO developed a public health approach, which involved use of standard regimens with little requirement for the monitoring that was being used at that time in developed country settings. Use of CD4 counts, particularly to select who should start ART, was encouraged but measures of viral load were very expensive in the context of low resource settings (the current fully loaded cost of a viral load test is the cost of around 8 months of ART for one person) and could not be used in most settings. At that time, however, increasing concerns were being expressed that widespread delivery of ART without use of viral load monitoring to identify people failing ART could lead to widespread development of drug resistance, with consequences for both the treated individuals and for the population, due to transmission of drug resistant HIV. There was no research available to evaluate the likely consequences of the ongoing roll-out strategy.

In previous work done by our group between 2003 and 2007, we had developed a stochastic computer simulation model of HIV progression and the effect of ART, based on our extensive work on studying HIV in cohort studies. The first paper from this model, published in 2007, made projections about the HIV population in the UK **[1]**. As a result of concerns about the roll out of ART in low-resource settings, we adapted our model to investigate the impact of lack of viral load monitoring on outcomes of ART in low resource settings **[2]** and included a transmission component to consider transmitted drug resistance **[3]**. This work helped us understand what the consequences of provision of ART without viral load monitoring were likely to be, in terms of patient survival and transmission of drug resistance. We showed that eventual use of viral load monitoring is important, particularly to avoid future widespread transmission of drug resistance, and that development of new tests which are not dependent on substantial laboratory infrastructure or highly trained staff should be a key research and development priority. However, we also showed that the impact on mortality of lack of viral load monitoring was likely to be modest in the short to medium term, relative to the mortality impact of failing to provide more widespread ART. Thus the message was to continue the roll-out without re-directing resources to viral load measurement but to encourage the development of cheaper tests.

Continuing our research in this areas, we are currently working with WHO on assessing the impact on transmission of HIV drug resistance of starting more people on ART earlier, and defining

threshold levels of transmitted drug resistance beyond which a change in public health policy is required. In further work using the model, we are collaborating with GSK Biologicals to model potential effects of their vaccines. We collaborate on this research with health economist colleagues at the London School of Hygiene and Tropical Medicine (Alec Miners) and, more recently, the University of York (Paul Revill).

3. References to the research

[1] Phillips AN, Sabin C, Pillay D, Lundgren JD. HIV in the UK 1980-2006: reconstruction using a model of HIV infection and the effect of antiretroviral therapy. HIV Medicine. 2007 Nov;8(8):536-46. http://dx.doi.org/10.1111/j.1468-1293.2007.00507.x

[2] Phillips AN, Pillay D, Miners A, Bennett D, Gilks CF, Lundgren JD. Outcomes from monitoring of patients on antiretroviral therapy in resource-limited settings with viral load, CD4 cell count, or clinical observation alone: a computer simulation model. Lancet**.** 2008 Apr 26;371(9622):1443-51. http://dx.doi.org/10.1016/S0140-6736(08)60624-8

[3] Phillips AN, Pillay D, Garnett G, Bennett D, Vitoria M, Cambiano V, Lundgren JD. Effect on transmission of HIV-1 resistance of timing of implementation of viral load monitoring to determine switches from first to second line antiretroviral regimens in resource-limited settings. AIDS. 2011 Mar 27;25(6):843-50. http://dx.doi.org/10.1097/QAD.0b013e328344037a

The research at this stage was directly funded by HEFCE (funding to Andrew Phillips).

4. Details of the impact

The research described above provided an evidence base to continue the rollout of ART in sub-Saharan Africa without diverting resources for ART to measures of viral load – a policy which had come under question in previous years. It was seen as critical to understand whether the consequences of roll out of ART without viral load monitoring were so severe (due to concerns over transmission of HIV drug resistance) as to mean that introduction of such testing should be prioritised over continued ART expansion by ART programmes. Our findings provided support for continued roll out in settings where viral load monitoring was not available. A comment paper written by colleagues from the Global Fund for HIV, TB and Malaria (the body which, along with U.S. President's Emergency Plan for AIDS Relief (PEPFAR), provided most funds for the ART roll-out) concluded that "*Phillips and colleagues' findings strengthen the policy consensus and WHO recommendation – so far based on individual patient outcomes and cost-effectiveness in the shorter term – that resource-poor countries need not delay ART roll-out because of limitations in laboratory capacity*" **[a]**.

The Director/Coordinator of Treatment and Prevention Scale-up at the WHO HIV Department at that time reports that "*the work... adapting the HIV synthesis to model the outcome of ART in low-income settings under different monitoring practices helped shape global ART roll-out policy and practice. Furthermore, because of its unique utility and approach, the modelling work and synthesis adaptations continue to be used to inform global policy development*" **[b]**.

Since 2008, the trajectory of the number of people on ART has increased, with 9.7 million people now on ART **[c]**. Almost all countries in sub-Saharan Africa (with the exceptions of South Africa and Botswana) have been providing ART without regular viral load monitoring. Point of care tests for viral load are now close to coming to market and WHO has started to encourage use of viral load testing in patient monitoring as resources allow, so long as this does not inhibit roll-out.

Our publications in 2008 and 2011 were written jointly with colleagues at WHO responsible for the public health approach **[d]**, and influenced their policy as described – i.e. to prioritise the continued expansion of roll-out of ART over introduction of viral load monitoring, but to encourage research and development of implementable viral load measurement technology. The two publications are officially approved WHO publications and our work has been cited in WHO guidelines. The 2008

WHO progress report "Towards Universal access: Scaling up priority HIV/AIDS interventions in the health sector" cites our publication from the previous year as providing support for WHO's recommendations on scaling up ART provision **[e]**. Furthermore, there were 11 references in total to the wider work of the HIV Epidemiology & Biostatistics Group of the Research Department of Infection & Population Health in the key WHO guideline "Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for a public health approach" **[f]**.

Our model has also been used by the Bill and Melinda Gates Foundation in their assessment of CD4 investment options, and was influential in them deciding to support development of a new point of care test. A program officer at the Foundation writes that: *"I have used your modeling analysis several times when we have been evaluating our options for CD4 investment. The impact of the Zyomyx test is a critical component of our decision making and we are constantly re-evaluating our decisions as we move forward, so your results have been considered again and again"* **[g]**.

5. Sources to corroborate the impact

[a] Korenromp EL, Fakoya A, Viisainen K. Scaling-up antiretroviral treatment in resource-poor countries: prioritization and choices. AIDS. 2011 Mar 27;25(6):857-9. http://dx.doi.org/10.1097/QAD.0b013e3283454401.

[b] Statement from Director of Treatment and Prevention Scale-up at the WHO HIV Department. Copy available on request.

[c] WHO Global update on HIV treatment 2013: results, impact and opportunities, June 2013. www.who.int/iris/bitstream/10665/85326/1/9789241505734_eng.pdf

[d] Gilks CF, Crowley S, Ekpini R, Gove S, Perriens J, Souteyrand Y, Sutherland D, Vitoria M, Guerma T, De Cock K. The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings. Lancet. 2006 Aug 5;368(9534):505-10. http://dx.doi.org/10.1016/S0140-6736(06)69158-7

[e] World Health Organisation. Towards Universal access: Scaling up priority HIV/AIDS interventions in the health sector. 2008 Progress Report. http://www.who.int/hiv/pub/2008progressreport/en/index.html (See page 35)

[f] World Health Organisation. Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for a public health approach. 2010 revision. http://www.who.int/hiv/pub/arv/adult2010/en/index.html

[g] Statement from Senior Program Officer at the Bill and Melinda Gates Foundation. Copy available on request.