Institution: University College London

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

Title of case study: CHER trial leads to changes in international guidelines on when to start HIV-infected infants on antiretroviral therapy

1. Summary of the impact

HIV-infected infants are at high risk of disease progression and death. Until 2008 guidelines recommended waiting until the infant displayed symptoms, or had a weakened immune system before starting treatment. The CHER trial found that starting infected infants on antiretroviral therapy as early as possible substantially reduced mortality compared with waiting until they developed symptoms or their immune system weakened. These results led quickly to changes in guidelines for treating HIV-infected infants issued by the US, World Health Organisation (WHO), Paediatric European Network for Treatment of AIDS (PENTA) and South Africa. These revised guidelines, if fully implemented along with early infant diagnosis, would reduce the number of infant deaths because of HIV by 76%, saving the lives of approximately 46,800 infants globally each year.

2. Underpinning research

The CHER trial aimed to see if giving a limited course of anti-retroviral therapy (ART) to babies as soon as possible after their HIV status was known would have a long-term health benefit, when compared with HIV-infected babies who are treated after they develop symptoms of HIV, or when their immune system has become weakened. Babies were randomised into three groups:

1. delayed ART until their immune system became weak (measured through a CD4 count)
2. immediate ART, which was then stopped when the babies reached the age of one year
3. immediate ART which was then stopped when they were two years old.

The trial began in August 2005. In June 2007 the IDMC recommended modifying the trial to stop enrolment into Arm 1, enrolled infants to be urgently assessed for ART, immediate release of the results of Arm 1 versus Arms 2 & 3, and trial follow-up to continue. This was because the interim analysis showed that immediate ART reduced mortality by 76%, and disease progression by 75% after a median follow-up of 32 weeks **[1,2]**.

Follow-up continued until September 2011, and the final results were presented at a conference in March 2012 **[4]**.

This was the first large randomised trial looking at when infants should start ART.

Based on the early results, we contributed to a costing study to look at the costs of early versus deferred ART for infants in South Africa. This found that early treatment was actually cheaper than deferred ART, mainly because of the reduction in hospitalisation **[3]**.

The trial was carried out in collaboration with the Perinatal HIV Research Unit of the University of Witwatersrand, and the Children's Infectious Disease Clinical Research Unit of Stellenbosch University, as part of the CIPRA-SA programme. Professors Di Gibb and Abdel Babiker from MRC Clinical Trials Unit (now part of UCL) played a major role in designing the study, were part of the Trial Steering and Management groups, advised on the execution of the trial, carried out and supervised the statistical analyses, and wrote the papers with their South African colleagues, Dr Avy Violari and Professor Mark Cotton.

A Wellcome Trust Fellowship has been awarded for Helen Payne to work with the Cape Town Group, supervised by Nigel Klein and Robin Callard from the UCL Institute of Child Health, Di Gibb

and Abdel Babiker from MRC CTU, now part of UCL, and Prof Mark Cotton from Cape Town. This work will provide very important data on the immunology of early ART initiation in babies as well as on stopping treatment. In addition following reports of the 'functional cure' of the Mississippi baby, further work is ongoing with collaborators in US as part of the 'cure' agenda.

3. References to the research

[1] Violari A, Cotton MF, Gibb DM, Babiker AG, Steyn J, Madhi SA, Jean-Philippe P, McIntyre JA; CHER Study Team. Early antiretroviral therapy and mortality among HIV-infected infants. N Engl J Med. 2008 Nov 20;359(21):2233-44. http://dx.doi.org/10.1056/NEJMoa0800971

[2] Violari A, Cotton M, Gibb D, Babiker A, Steyn J, Jean-Phillip P, McIntyre J, on behalf of the CHER Study Team. Antiretroviral therapy initiated before 12 weeks of age reduces early mortality in young HIV-infected infants: Evidence from the children with HIV early antiretroviral therapy (CHER) study. Special session: 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention. 2007. Abstract no. WESS103. http://www.iasociety.org/Default.aspx?pageId=11&abstractId=200705557

[3] Meyer-Rath Gesine, Violari A., Cotton M., Ndibongo B., Brennan A., Long L., Panchia R., Coovadia A., Gibb D.M., Rosen S., (2010). The cost of early versus deferred paediatric antiretroviral treatment in South Africa: A comparative economic analysis of the first year of the Children with HIV Early Antiretroviral Therapy (CHER) trial. XVIII International AIDS Conference, Vienna, Abstract no. **THLBB103.** http://pag.aids2010.org/Abstracts.aspx?AID=17823

[4] Cotton M, Violari A, Gibb D, Otwombe K, Josipovic D, Panchia R, Jean-Philippe P, Handelsman E, McIntyre J, Babiker A. Early ART Followed By Interruption is Safe & Associated With Better Outcomes than Deferred ART: Final Results From the 6-Year Randomized CHER (Children with HIV Early antiRetroviral) Trial in South Africa. 19th Conference on Retroviruses and Opportunistic Infections. 2012. Available on request.

[5] Cotton M, Violari A, Otwombe K, Panchia R, Dobbels E, Rabie H, Josipovic D, Liberty A, Lazarus E, Innes S, van Rensburg A, Pelser W, Truter H, Madhi S, Handelsman E, Jean-Philippe P, McIntyre J, Gibb DM. Early time-limited antiretroviral therapy versus deferred therapy in South African infants infected with HIV: results from the children with HIV early antiretroviral (CHER) randomised trial. Lancet 382. 2013. http://dx.doi.org/10.1016/S0140-6736(13)61409-9

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4. Details of the impact

HIV-infected infants are at high risk of disease progression and death. But initiating them on lifelong antiretroviral therapy (ART) is problematic because:

- it is a lifelong commitment
- it costs money
- the drugs can have side effects
- the earlier infants start treatment the more time there is for resistance to develop.

Until 2008, national and international guidelines recommended initiation of antiretroviral therapy on the basis of a low CD4 percentage or count, a high viral load, or the presence of clinical symptoms,

whereas the treatment of asymptomatic infants with high CD4 values was not mandated.

The early results of CHER were released at the 4th International AIDS Society Conference on Pathogenesis, Treatment and Prevention in July 2007. In response to these results, a number of key national and international guidelines were changed.

In February 2008 US national guidelines were changed to recommend immediate treatment of HIV-infected infants **[a]**.

WHO held a meeting in April 2008 to look at the evidence from CHER in relation to their guidelines, and launched new interim guidelines in June 2008, recommending immediate treatment of HIV-infected infants. These were then incorporated into the full guidelines when they were revised in 2010 **[b]**.

The Paediatric European Network for Treatment of AIDS (PENTA) changed their guidelines to recommend immediate treatment of HIV-infected infants in November 2008 **[c]**.

WHO guidelines are very influential for national HIV policy, particularly in African countries, where most HIV-positive infants live. A survey of national HIV policymakers, carried out in 2008, found that WHO was an important and frequent source of information to inform HIV policymaking in Africa **[d]**. Therefore the incorporation of recommendations from the CHER trial into WHO policy has had a knock-on effect on national guidelines in Africa. Following the changes to WHO guidance, individual countries began to follow suit by changing their national guidelines. For example, in South Africa the Essential Drug List Committee approved the recommendation in November 2008, and it was included in the national guidelines issued in December 2010, following the costing study **[e]**. The Malawi Ministry of Health updated their guidelines in April 2008 **[f]**, and the Uganda Ministry of Health updated their guidelines in June 2009 on when to start infants on treatment **[g]**.

National guidelines are very important determinants of the treatments given in practice in low-income settings. In many African settings most children are treated by clinical officers rather than doctors. These clinical officers have less training than doctors, and therefore use national guidelines as the basis of how they treat patients to a much greater extent than doctors in high-income countries.

One paediatrician working in Zambia describes the impact of the trial as follows: "*These changes were quickly adapted by many African countries including Zambia, a step that enabled many HIV infected children to be started early on ART and not only have these children survived but they have been able to lead a relatively normal childhood. Currently it is estimated that about 43,000 children 0-14 years old are receiving ART in Zambia, a 50% increase from the 21,120 in 2009 (WHO, UNAIDS, UNICEF Progress Report 2010). The impact of the CHER trial has not only been on outcome of children but the findings have also helped push for improved laboratory diagnostic services in order to initiate early treatment in as many infants and children as possible in Zambia…Deaths from HIV/AIDS have dramatically dropped in infants and children, as most of the children are identified early and commenced on treatment. The CHER trial results have had a great impact on treatment of HIV infected infants and children, subsequently on survival, hospital admissions and ultimately cost of treatment and care for HIV infected infants and children"* **[h]**.

As the results have led to changes in guidelines for HIV-infected infants worldwide, the research has had a global impact on infants living with HIV in both high and low-income settings. It is difficult to say exactly how many children have benefited as a result of this research, as the routine data collected by most countries does not disaggregate ART coverage figures into small enough age-bands. We can, however, extrapolate how many lives could potentially be saved based on global figures. Each year around 390,000 children are infected with HIV **[i]**. The vast majority of these children were vertically-infected infants. CHER found that early ART reduced infant mortality from 16% to 4%. If we assume that the WHO guidelines were fully implemented worldwide, the results of this trial would lead to around 46,800 lives being saved each year (although the number of

infected infants will decline with the scale-up of Prevention of Mother To Child Transmission programmes).

The costing study found that early ART for infants had lower costs per child to the health system than deferred ART or the strategy that was routine care at the time in South Africa ($1,387 vs $2,440 vs $3,008 respectively) **[ref 3, above]**. This means that the health system in South Africa (and possibly other settings) will benefit through reduced costs of treating HIV-infected infants, as they require less hospitalisation. In 2011 there were approximately 29,000 new infections in children in South Africa. If all these newly-infected infants had been treated early, it could save the South African health system as much as 47 million USD.

5. Sources to corroborate the impact

[a] US national guidelines: Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Rockville, MD: National Institutes of Health, US, 2008. http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf

[b] WHO guidelines: WHO (2010): ANTIRETROVIRAL THERAPY FOR HIV INFECTION IN INFANTS AND CHILDREN: TOWARDS UNIVERSAL ACCESS Recommendations for a public health approach 2010 revision. http://whqlibdoc.who.int/publications/2010/9789241599801_eng.pdf

[c] PENTA guidelines: PENTA Steering Committee (2009): PENTA 2009 guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection. *HIV Medicine* 10: 591–613 DOI: 10.1111/j.1468-1293.2009.00759.x http://www.pentatrials.org/HIV_759.pdf

[d] Parkhurst JO, Hyde A, South A, Brehmer L, Miller A, Newell JN. Improving communication of research findings – identifying the sources of information most important to national disease control officers in low and middle income countries. Tropical Medicine and International Health 2010;15(10):1252-55. http://dx.doi.org/10.1111/j.1365-3156.2010.02599.x

[e] Department of Health, Republic of South Africa (2010): The South African Antiretroviral Treatment Guidelines. http://www.uj.ac.za/EN/CorporateServices/ioha/Documentation/Documents/ART%20Guideline.pdf

[f] Malawi Ministry of Health (2008): Treatment of AIDS: Guidelines for the use of antiretroviral therapy in Malawi. Third Edition, April 2008. http://www.basics.org/documents/ART_Guidelines_Malawi.pdf (page 29)

[g] Uganda Ministry of Health (2009): National Antiretroviral Treatment Guidelines for Adults, Adolescents, and Children http://www.idi-makerere.com/docs/guidelines%202009.pdf (page 22)

[h] Letter from Paediatrician, University Teaching Hospital, Lusaka, Zambia. Copy available on request.

[i] http://www.unaids.org/believeitdoit/get-the-facts.html