

<p>Institution: King's College London</p>
<p>Unit of Assessment: 1 - Clinical Medicine</p>
<p>Title of case study: Fewer deliveries by caesarean section in HIV-infected women and less mother-to child transmission due to improved antiretroviral treatment during pregnancy</p>
<p>1. Summary of the impact</p> <p>King's College London (KCL) research has had an major impact on guidelines in the UK, USA, Sweden and worldwide – through the World Health Organization (WHO) – on managing HIV in pregnancy to balance the risk of transmitting HIV from mother-to-child against the toxicities of antiretroviral therapy and the need for Caesarean section. Specifically, KCL research led to guidance on when HIV-infected women should begin antiretroviral treatment and at what viral load they can deliver vaginally to minimise mother-to-child transmission (MTCT). This guidance has led to fewer Caesarean sections (a less acceptable mode of delivery compared to natural vaginal delivery, especially in many ethnic minority groups), a drop in MTCT rates in England and Ireland, and better advice to healthcare practitioners and patients.</p>
<p>2. Underpinning research</p> <p>KCL research on mother-to-child transmission (MTCT) of HIV is led by Dr de Ruiter (1994 to present).</p> <p>HIV transmission from mother to child: The three ways of avoiding MTCT are delivering the baby by pre-labour Caesarean section (PLCS), avoiding breastfeeding, and using antiretroviral drug therapy. Since 1994 treating HIV-infected pregnant women with antiretrovirals and delivering their babies by PLCS has lowered rates of MTCT from 35% to less than 2% in countries where these treatments are available. If only one antiretroviral is used, HIV can rapidly mutate and become resistant to that drug. Highly active antiretroviral therapy (HAART), a combination of three or more antiretrovirals, can prevent this.</p> <p>KCL advice to the National Study of HIV in Pregnancy and Childbirth (NSHPC): In 2006/2007, de Ruiter advised NSHPC on research on two important areas where guidelines for management of HIV in pregnancy and mother-to-child transmission were lacking:</p> <ul style="list-style-type: none"> • Vaginal delivery for pregnant women receiving HAART • Zidovudine monotherapy and PLCS. <p>KCL research on HIV-infected women delivering vaginally: The KCL research group, with collaborators, investigated whether or not vaginal delivery by HIV-infected women receiving HAART increased MTCT rates. The results, published in 2008 [1], showed the MTCT rate for HIV-infected women on HAART who delivered vaginally was the lowest ever reported (0.1%). The findings established the new 2008 British HIV Association (BHIVA) guidelines on effective pregnancy interventions which included vaginal delivery as an option for HIV-infected pregnant women for the first time.</p> <p>KCL research on antiretroviral drugs: Research led by the KCL group, and involving colleagues at Imperial College and St George's Hospital, showed that when zidovudine monotherapy was used in accordance with 2008 BHIVA guidelines there was no evidence of emerging drug resistance [2] or minor resistant species [3]. The research also showed that zidovudine monotherapy with PLCS did not result in higher rates of MTCT [2].</p> <p>The physiological changes of pregnancy can alter how drugs work. US studies suggested that the dose of the protease inhibitor lopinavir needed to prevent HIV replicating should be increased in pregnancy. The KCL group's work on virological responses to lopinavir in HIV-infected pregnant women at Guy's & St Thomas' Hospital found that in pregnancy the standard dose was sufficient, which means a higher dose is not required [4,5].</p> <p>There were also concerns about the potential toxicity of nevirapine in pregnancy. Two KCL-led studies involving Dr de Ruiter, Professor P Easterbrook and Dr J Welch, with collaborators at St</p>

Mary's Hospital [6, 7] and at St Bartholomew's Hospital [7], showed that the degree of toxicity of nevirapine in pregnant women is no more than that in non-pregnant women. This finding is significant because nevirapine is widely used in developing countries.

KCL research on pregnant HIV-infected teenagers in the UK: KCL-led research on pregnancy in HIV-infected teenage girls showed that the outcomes were comparable to those of HIV-infected adult women [8], and these findings influenced the BHIVA 2012 and the USA Department of Health and Human Services (DHHS) 2012 guidelines.

3. References to the research *Bold names denote KCL authors*

1. Townsend CL, Cortina-Borja M, Peckham CS, **de Ruiter A**, Lyall H, Tookey PA. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000–2006. *AIDS*. 2008;22:973–81.
2. **Larbalestier N, Mullen J, O'Shea S, Cottam F**, Sabin CA, **Chrystie IL, Welch J, Zuckerman M**, Hay P, Rice P, Taylor GP, **de Ruiter A**. Drug resistance is uncommon in pregnant women with low viral loads taking zidovudine monotherapy to prevent perinatal HIV transmission. *AIDS*. 2003;17:2665–7.
3. **Read P, Costelloe S, Mullen J, O'Shea S, Lyons F**, Hay P, **Welch J, Larbalestier N**, Taylor G, **de Ruiter A**. New mutations associated with resistance not detected following zidovudine monotherapy in pregnancy when used in accordance with British HIV Association guidelines. *HIV Med*. 2008;9:448–51.
4. **Read PJ**, Mandalia S, Khan P, Harrison U, Naftalin C, Gilleece Y, Anderson J, Hawkins DA, Taylor GP, **de Ruiter A**. London Perinatal Research Group. When should HAART be initiated in pregnancy to achieve an undetectable HIV viral load by delivery? *AIDS*. 2012;26:1095–103.
5. **Lyons F, Lechelt M, de Ruiter A**. Steady-state lopinavir levels in third trimester of pregnancy. *AIDS*. 2007;21:1053–4.
6. **Edwards SG, Larbalestier N**, Hay P, **de Ruiter A, Welch J**, Taylor GP, **Easterbrook P**. Experience of nevirapine use in a London cohort of HIV-infected pregnant women. *HIV Med*. 2001;2:89–91.
7. **Natarajan U**, Pym A, **McDonald C**, Velisetty P, Edwards SG, Hay P, **Welch J, de Ruiter A**, Taylor GP, Anderson J. Safety of nevirapine in pregnancy. *HIV Med*. 2007;8:64–9.
8. **Elgalib A**, Hegazi A, **Samarawickrama A**, Roedling S, Tariq S, Draeger E, Hemelaar J, Rathnayaka T, Azwa A, Hawkins D, Edwards S, Perez K, Russell J, Wood C, **Poulton M**, Shah R, Noble H, Rodgers M, Taylor GP, Anderson J, **de Ruiter A**. Pregnancy in HIV-infected teenagers in London. *HIV Med*. 2011;12:118–23.

4. Details of the impact

Marked rise in vaginal delivery by HIV positive women: The improvement in vaginal delivery rates for HIV-infected women is the greatest impact resulting from this research on antiretroviral treatments in pregnancy. The percentage of HIV-infected women in the UK and Ireland delivering vaginally rose from 14% in 2000–2006 to 31% in 2007–2011 (Section 2). This improvement in vaginal delivery rates for HIV-infected women is due to the better understanding of the use of antiretroviral drugs in pregnancy in which KCL research played a major role (Section 2). In the period 2007–2011, women commenced antiretroviral therapy earlier in pregnancy compared to 2000–2006. Antiretroviral therapy started at 23 rather than 26 weeks.

Further fall in mother-to-child transmission rates: The overall HIV mother-to-child transmission rate for the UK and Ireland fell from 1.2% in 2000–2006 to 0.5% in 2007–2011 (Section 2).

Findings used in national guidelines for management of HIV infection in pregnant women:

The KCL research covered in section 2 has had a considerable impact on changing approaches to managing HIV infection in pregnant women. Based on KCL research, the 2008 British HIV Association (BHIVA) guidelines [9] recommended that HIV-infected pregnant women should be treated with short-term antiretroviral therapy if their viral load was above 10,000 copies/ml. Standard antiretroviral treatment should begin in the second trimester with the aim of reducing the viral load to less than 50 copies/ml before delivery. Women with less than 50 copies/ml at full term could deliver vaginally.

BHIVA guidelines recommended that women who require treatment for HIV for their own health should be treated with an antiretroviral regimen regardless of viral load. Based on KCL research, the BHIVA guidelines also allow zidovudine monotherapy as an option for pregnant women with certain immunological and virological issues. Based on further KCL research, the 2012 BHIVA guidelines [10] advanced the date for starting HAART in pregnancy (Section 2).

The BHIVA guidelines are widely distributed – HIV Medicine distributed print copies of the 2008 and 2012 BHIVA guidelines to all subscribers – and are also widely accessed online. As of 11 March 2013, the 2008 guidelines had been accessed 18,157 times (16,242 individuals) and the 2012 guidelines 9,051 times (8,258 individuals).

Findings used in international and national treatment publications: This KCL research has had a very significant impact on international and national guidelines for treating HIV-infected pregnant women and preventing MTCT.

Dr de Ruiter was the chair and lead author of the British HIV Association (BHIVA) 2008 pregnancy guidelines [9] which allowed vaginal delivery as an option for HIV positive women, whereas previously PLCS was recommended for all. The National Health Service accredited the guidelines in July 2012. KCL research findings on doses of lopinavir in treatment of HIV in pregnant women (Section 2) were incorporated in the 2008 and 2012 BHIVA guidelines [9,10]. Dr de Ruiter was the chair of the British HIV Association (BHIVA) and Children’s HIV Association (CHIVA) position statement on infant feeding in the UK 2011 [11,12].

KCL findings have had considerable impact on other national and international guidelines. These include 2010 WHO recommendations for a public health approach to antiretroviral drugs for treating pregnant women and preventing HIV infection in infants [13]. The revision of the clinical protocol for the WHO European region 2012 used the findings of KCL research to recommend zidovudine monotherapy as an option for preventing HIV transmission from HIV-infected mothers to their infants [14]. The findings also have a considerable impact on the Royal College of Obstetricians and Gynaecologists guide on management of HIV in pregnancy [15], the Swedish guidelines on treatment of HIV in pregnancy [16] and USA Department of Health and Human Services (DHHS) recommendations [17].

Findings used in further work on guidelines: KCL research underpinned an investigation on differences and similarities between the US DHHS perinatal guidelines and the BHIVA 2012 pregnancy guidelines [18].

Public-facing communication: Patient information leaflets produced by NAM (National AIDS Manual) [19] refer to KCL research on MTCT rates and HAART. The HIV treatment information base (i-base.info) also uses the findings of KCL research [20].

5. Sources to corroborate the contribution, impact or benefit

National guidelines based on KCL group’s work

9. **de Ruiter A**, Mercey D, Anderson J, Chakraborty R, Clayden P, Foster G, Gilling-Smith C, Hawkins D, Low-Beer N, Lyall H, O’Shea S, Penn Z, Short J, Smith R, Sonecha S, Tookey P, Wood C, Taylor G. British HIV Association and Children’s HIV Association guidelines for the management of HIV infection in pregnant women 2008. *HIV Med.* 2008;9:452–502. (Cites ref

Impact case study (REF3b)

[1] p.488, ref [7] p.470).

<http://www.bhiva.org/documents/Guidelines/Pregnancy/2008/PregnancyPub.pdf>

10. Taylor GP, Clayden P, Dhar J, Gandhi K, Gilleece Y, Harding K, Hay P, Kennedy J, Low-Beer N, Lyall H, Palfreeman A, Tookey P, Welch S, Wilkins E, **de Ruiter A**. British HIV Association guidelines for the management of HIV infection in pregnant women 2012. *HIV Med.* 2012;13 Suppl 2:87–157. (Cites ref [1] p.137; ref [9] p.139; ref [5] p.141)

http://www.bhiva.org/documents/Guidelines/Pregnancy/2012/hiv1030_6.pdf

11. British HIV Association and Children's HIV Association position statement on infant feeding in the UK 2011. *HIV Med.* 2011;12:389–93. (Cites ref [1] p.392)

de Ruiter's leadership of national scientific group

12. BHIVA/CHIVA Guidelines Writing Group. Taylor GP, Anderson J, Clayden P, Gazzard BG, Fortin J, Kennedy J, Lazarus L, Newell ML, Osoro B, Sellers S, Tookey PA, Tudor-Williams G, Williams A, **de Ruiter A**.

International guidelines based on KCL group's work

13. World Health Organization, 2010. Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants. Recommendations for a public health approach:

http://whqlibdoc.who.int/publications/2010/9789241599818_eng.pdf (Cites ref [1] p.101)

14. World Health Organization, 2012. European region 2012 update on Prevention of HIV transmission from HIV-infected mothers to their infants.

http://www.euro.who.int/_data/assets/pdf_file/0007/159973/PMTCT_20120302.pdf (Cites ref [1] p.31, ref [6] p.45, ref [7] p.45)

15. Royal College of Obstetricians and Gynaecologists, 2011. Management of HIV in Pregnancy.

http://www.rcog.org.uk/files/rcog-corp/uploaded-files/GtG_no_39_HIV_in_pregnancy_June_2010_v2011.pdf (Cites ref [1] p.24)

16. Swedish Guidelines 2011: Navér L, Albert J, Belfrage E, Flamholc L, Gisslén M, Gyllensten K, Josephson F, Karlström O, Lindgren S, Pettersson K, Svedhem V, Sönnernborg A, Westling K, Yilmaz A, Swedish Reference Group for Antiviral Therapy. Prophylaxis and treatment of HIV-1 infection in pregnancy: Swedish recommendations 2010. *Scand J Infect Dis.* 2011;43:411–23 (Cites ref [1] p.412)

17. Department of Health and Human Services USA, 2012. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States.

<http://aidsinfo.nih.gov/contentfiles/lvguidelines/perinatalgl.pdf> (Cites ref [1] pp.A-4,B-16,C-10,D-35,G-10, ref [2] p.D-37, ref [3] p.D-37, ref [8] p.C-5)

Findings used in further international work on guidelines

18. Michelle Giles (Australia): HIV and pregnancy: how to manage conflicting recommendations from evidence-based guidelines. *AIDS.* 2013;27:857–62. (Cites ref [1] p.857, 860)

Public-facing communication

19. National AIDS Manual AIDSmap patient advice pages: <http://www.aidsmap.com/When-to-start-treatment/page/1324529/> (Cites <http://www.aidsmap.com/Choosing-a-regimen/page/1324530/>; <http://www.aidsmap.com/Types-of-regimen/page/1323200/>)

20. HIV I-base leaflets:

When should HAART be initiated in pregnancy to achieve an undetectable viral load? <http://i-base.info/htb/10234> Posted 2 April 2012 (Cites ref [4])