Institution: Imperial College London

Unit of Assessment: 01 Clinical Medicine

Title of case study: Defining the Role of Antiretroviral Therapy for Primary or Recent HIV Infection

1. Summary of the impact (indicative maximum 100 words)

The SPARTAC study (**S**hort **P**ulse **A**nti-**R**etroviral **T**herapy **a**t HIV **C**onversion) was a randomised clinical trial of short (12 weeks) or long (48 weeks) pulsed antiretroviral therapy (ART) at primary or recent HIV infection, compared to deferred therapy (standard of care). The trial has shown a significant effect of 48 weeks ART, compared to deferred therapy; 12 weeks ART had no effect. This definitive result from the SPARTAC trial has informed HIV treatment guidelines nationally and internationally; patients identified with primary or recent HIV infection are now recommended to commence ART, based in whole or part on the evidence arising out of SPARTAC. As a consequence of the SPARTAC trial, it is no longer ethical to undertake research amongst individuals with recent HIV infection without offering immediate ART.

2. Underpinning research (indicative maximum 500 words)

Key Imperial College London researchers:
Professor Jonathan Weber, Vice Dean, Faculty of Medicine (1991-present)
Dr Sarah Fidler, Reader in Communicable Diseases and Honorary Consultant Physician (1997-present)
Professor Myra McClure, Professor of Retrovirology (1991-present)

The course of HIV infection has been radically transformed by combination anti-retroviral therapy (ART). Patients chronically infected by HIV had a median life expectancy of 12 years prior to ART, now on ART they have an estimated 40 years survival after diagnosis, with good quality of life, approximating to a normal life span. ART, with its dramatic impact on morbidity and mortality from HIV infection, does not eradicate the virus, necessitating life-long therapy. If ART is ceased, then HIV replication recommences immediately from the proviral DNA reservoir in long-lived cells.

In 2000, anecdotal reports on very small numbers of non-randomised patients suggested that early use of ART at Primary HIV infection (PHI) might preserve HIV-specific T-cell immunity, which is otherwise lost after HIV infection (1). This is believed to be due to direct viral killing of CD4+ T-cells. Imperial researchers subsequently hypothesised in 2000 that immediate intervention with ART at the time of PHI, when immune function is still preserved, might protect CD4 cells from HIV-mediated killing via ART-induced suppression of replication, leading to a long-term impact on the patient's immunological control of HIV replication. In particular, we hypothesised that even a short pulse of ART at PHI might have a long term benefit through suppressing HIV replication at a critical time of primary infection, when the immunity is still developing and the proviral DNA reservoir is still small.

As the safety and potential efficacy of a short pulse of ART at PHI was unknown, we embarked on a pilot study in the UK (2000-2004), funded by the Wellcome Trust Programme grant jointly held by Phillips and Weber, as a formal collaboration between Imperial College and the University of Oxford. The Philips laboratory contributed cellular immunology expertise and Imperial researchers contributed the clinical trial design, implementation, humoral immunity, biobank and viral genotyping. Over 100 participants were enrolled into this pilot which demonstrated that a pulse of 12 weeks ART was safe, tolerable, did not induce resistance and could be safely stopped; ART with 4 drugs added toxicity and reduced tolerability without increasing efficacy (2, 3, 4). Based on this pilot, a definitive randomised controlled trial, SPARTAC, was developed by Imperial researchers with the MRC Clinical Trials Unit, and subsequently funded by two Wellcome Trust strategic awards (PI, Weber, Imperial) between 2004-2008 and then 2008-2012.The distribution of research work between the universities in the full trial was as in the pilot.

SPARTAC enrolled 371 individuals with recent HIV infection across 3 continents with median 4.2 years follow up, randomised 1:1:1 to 12 week ART, 48 week ART or no therapy; the primary outcome was chosen as time to CD4 decline to 350 – a clinically relevant measure of HIV progression. The SPARTAC trial was the first and remains the only randomised clinical trial which was designed and powered to address definitively the role of immediate ART in PHI using validated surrogate markers of disease progression capable of informing clinical care.

Two contemporary and competing clinical trials of ART at PHI failed to deliver significant results; the US ACTG 5217 trial was terminated prematurely without result owing to a design flaw and the European PRIMO trial was underpowered and hence could not demonstrate a significant result. The main SPARTAC trial result was presented at the 2011 International AIDS conference in Rome and has since been published by the New England Journal of Medicine (5).

The SPARTAC trial compared the outcome from a total of 366 eligible participants (60% male) randomized to either 48 weeks of immediate ART; (ART48 n=123), or 12 weeks of immediate ART (ART12 n=120) or standard of care – no therapy; (SOC n=123) with average follow up 4.2 years. Participants were enrolled at 35 sites across 8 countries including; UK, Eire, Italy, Spain, Uganda, S Africa, Australia and Brazil. 50% of ART48 participants reached composite primary endpoint compared to 61% in each of ART-12 and SOC. The study showed that a 48-week ART course in PHI delayed disease progression, reduced subsequent HIV RNA levels for up to 6 months after the cessation of therapy and increased CD4 cell count by 138 cells over 4.2 years. Scientifically this study has refocused attention on the potential for manipulating the balance between viral replication and anti-viral immunity at primary HIV infection, given that the ART48 gave a long-lasting reduction in HIV viral load, after the cessation of therapy. The data have also contributed to the evidence base for universal HIV treatment at all stages of HIV infection. Finally, the potency of intervention at PHI, demonstrated in SPARTAC, has formed the basis for new research on HIV eradication.

3. References to the research (indicative maximum of six references)

(1) Oxenius, A., Price, D.A., Easterbrook, P.J., et al. (2000). Early highly active antiretroviral therapy for acute HIV-1 infection preserves immune function of CD8+ and CD4+ T lymphocytes. *Proc Natl Acad Sci U S A*, 97, 3382-3387. DOI. Times cited: 273 (as at 8th November 2013 on ISI Web of Science). Journal Impact Factor: 9.68

(2) Fidler, S., Oxenius, A., Brady, M., Clarke, J., Cropley, I., Babiker, A., Zhang, H.T., Price, D., Phillips, R., & Weber, J. (2002). Virological and immunological effects of short-course antiretroviral therapy in primary HIV infection. *AIDS*, 16 (15), 2049-2054. DOI. Times cited: 43 (as at 8th November 2013 on ISI Web of Science). Journal Impact Factor: 6.24

(3) Fidler, S., Fox, J., Touloumi, G., Pantazis, N., Porter, K., Babiker, A., Weber, J. (2007). Slower CD4 cell decline following cessation of a 3 month course of HAART in primary HIV infection: findings from an observational cohort. *AIDS*, 21 (10), 1283-1291. DOI. Times cited: 16 (as at 8th November 2013 on ISI Web of Science). Journal Impact Factor: 6.24

(4) Fox, J., Scriba, T.J., Robinson, N., Weber, J.N., Phillips, R.E., Fidler, S. (2008). Human immunodeficiency virus (HIV)-specific T helper responses fail to predict CD4+ T cell decline following short-course treatment at primary HIV-1 infection. *Clin Exp Immunol*, 152 (3), 532-537. DOI. Times cited: 1 (as at 8th November 2013 on ISI Web of Science). Journal Impact Factor: 3.36

(5) SPARTAC Trial Investigators, Fidler, S., Porter, K., Ewings, F., Frater, J., Ramjee, G., Cooper, D., Rees, H., Fisher, M., Schechter, M., Kaleebu, P., Tambussi, G., Kinloch, S., Miro, J.M., Kelleher, A., McClure, M., Kaye, S., Gabriel, M., Phillips, R., Babiker, A., Weber, J. (2013). Short-course antiretroviral therapy in primary HIV infection. *N Engl J Med*, 368 (3), 207-217. DOI. Times cited: 7 (as at 8th November 2013 on ISI Web of Science). Journal Impact Factor: 53.3

Key funding:

- Wellcome Trust(1999-2004, £2.4million) Co-Principal Investigators (Co-PIs) J. Weber, R. Phillips (Oxford), HIV Immunity and Evasion

- Wellcome Trust (2003-2008, £5.8M; 2009-2012, £1.5million) PI J. Weber, Short Pulse Anti-Retroviral Therapy at HIV Conversion (SPARTAC) trial

4. Details of the impact (indicative maximum 750 words)

Impacts include: health and welfare, public policy and services, practitioners and services
Main beneficiaries include: patients, BHIVA, international guideline bodies, NHS

Following the presentation of the results of the SPARTAC trial in July 2011, the UK British HIV Association (BHIVA) guidelines writing committee altered their recommendation for the optimum management of individuals with asymptomatic or less severe symptoms associated with primary HIV infection [1].

The use of ART at primary HIV infection has now become an auditable outcome for the UK standards recommendation, encouraging clinicians nationally to discuss the use of immediate ART for all individuals presenting with PHI.

BHIVA guidelines suggest that the following should be discussed with those presenting with a very short test interval (<=12 weeks) or evidence of acute HIV infection (such as rash, fever, weight loss, diarrhoea etc). The guidelines state:

1. A 48 week course of ART showed a benefit in delaying CD4 decline (there was no such benefit from 12 week ART) in those individuals presenting within 12 weeks of infection.

2. No study has examined whether ART started soon after seroconversion should be continued long-term, but most clinicians would recommend that ART should be continued once it has been started. Initiation of a PI-based regimen is recommended if therapy is started prior to the availability of a genotype result based on the prevalence of transmitted rates of drug resistance in the UK. In addition, this is also likely to lead to a more rapid reduction in infectivity because free virions are not infectious, which may be particularly relevant in PHI.

3. There is no specific evidence to support the role of ART in PHI to prevent onward transmission of virus but there is little reason to consider that ART is any less effective in reducing infectivity at this time, so long as viral suppression has been achieved [1; see pages 24-25].

The HIV treatment guidelines in the USA also reference the SPARTAC trial as evidence for the benefit of ART in primary or recent HIV infection; the Australian guidelines specifically reference the SPARTAC trial in their most recent publication [2-3]. The trial has received wide news coverage from the press and patient information groups [4-5].

The influence of the SPARTAC and the subsequent uptake of the revised treatment guidelines result can be seen from an analysis of the proportion of individuals starting ART at primary HIV infection in the UK, drawn from the MRC-funded UK National Register of HIV Seroconverters. Data covering ART prescribing across the UK from this observational cohort have shown a progressive increase in ART as shown below, where for the years 2008-2013, the percentage of individuals presenting with PHI offered immediate ATR has increased; in particular, there was a step change of 42% increase in ART prescribing at PHI following the SPARTAC trial report in July, 2011. As the revised guidelines cite only the SPARTAC results as the key information underpinning the evidence for ART at PHI, we are confident that this treatment effect is a direct consequence of our trial.

2008-2009	2009-2010	2010-2011	2011-2013
8.3%	16.9%	14.4%	34.7%

At Imperial College NHS Trust a new PHI pathway clinical service has been established and on the back of this the proportions of recently infected individuals choosing immediate ART has similarly

increased since the main trial reported in 2011. This clinic is regularly audited.

SPARTAC has had other and wider impacts on HIV infection globally. It has placed primary or acute HIV infection back on the public health agenda as a potential for long-lasting intervention (for example, see ref 6). Owing to the clear advantage of early therapy, SPARTAC has underpinned the move to early diagnosis and initiation of ART in order to reduce HIV transmission, now the subject of an international Imperial/LSH&TM-led clinical trial (www1.imperial.ac.uk/.../hiv_trials/hiv_prevention_technologies/popart).

5. Sources to corroborate the impact (indicative maximum of 10 references)

[1] British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012. HIV Med. 2012 Sep;13, Suppl 2:1-85. http://www.bhiva.org/documents/Guidelines/Treatment/2012/hiv1029_2.pdf (archived on 8th November 2013)

[2] US guidelines reference the SPARTAC trial as evidence for the benefit of ART at primary or recent HIV infection: http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/20/acute-and-recent--early---hiv-infection (see page I-3). Archived on 8th November 2013.

[3] Australian guidelines reference the SPARTAC trial as evidence for the benefit of ART at primary or recent HIV infection: http://ashm.org.au/default2.asp?active_page_id=587 (archived on 8th November 2013)

[4] HIV Patient information sites carried extensive coverage of the impact of the SPARTAC trial:

- http://www.aidsmap.com/Short-course-HAART-in-primary-infection-British-study/page/1413553/ (archived on 8th November 2013)
- http://www.poz.com/rssredir/articles/treat_early_761_23386.shtml (archived on 8th November 2013)
- http://www.thebodypro.com/content/63690/spartac-trial-treatment-in-primary-infection-for-4.html (archived on 8th November 2013)
- http://www.natap.org/2011/IAS/IAS_45.htm (archived on 8th November 2013)
- http://i-base.info/htb-south/1528 (archived on 8th November 2013)

[5] The SPARTAC trial was heavily reported in the general and medical press:

- http://www.bbc.co.uk/news/health-21040256 (archived on 8th November 2013)
- http://depts.washington.edu/hivaids/arvrx/case4/discussion.html (archived on 8th November 2013)
- http://aids-clinical-care.jwatch.org/cgi/content/full/2013/118/1 (archived on 8th November 2013)

[6] Lichterfeld, M., Rosenberg, E. (2013). Acute HIV Infection: A call to action. *Ann Int Med*, 159, 425-427. DOI