April 2002 Interdepartmental Public Health HIV/AIDS Journal Club

The fourth session of the 2002 series of HIV/AIDS Journal Club meetings was held on 5 April in the Steve Biko Lecture Theatre, Nelson R Mandela School of Medicine. Co-hosted by the Department of Community Health, HIVAN and the Harvard Enhancing Care Initiative (ECI), the meeting was opened by Dr Robert Pawinski, who welcomed all present and introduced the two guest presenters: Professor Sharon Cassol, Honourary Professor in Anatomical Pathology at UND Medical School and Principal Investigator in the Africa Centre's Molecular Virology and Bioinformatics Unit, and doctoral student Michelle Tarin, Senior Laboratory Technologist, also from the Unit.

Michelle Tarin presented on two journal articles:

1.) Polis M A, Sidorov I A, Yoder C, Jankelevich S, Metcalf J, Mueller B U, Dimitrov M A, Pizzo P, Yarchoan R and Dimitrov D S: **Correlation between reduction in plasma HIV-1 RNA concentration one week after the start of anti-retroviral treatment and longer term efficacy.** The Lancet 2001 Nov 24; 358 (9295):1760-5

In this study, the investigators attempted to determine whether early assessment of ARV drug efficacy is important for the prevention of the emergence of drug-resistant virus and unnecessary exposure to ineffective drug regimens. Using current US guidelines, measurements of plasma HIV-1 RNA concentrations four to eight weeks after the start of therapy were taken. A change of therapy was indicated if plasma HIV-1 RNA reduced <0.5-0.75 log after four weeks, or <1.00 log reduction by eight weeks. The authors postulated that the initial slopes of HIV-1 concentration changes during the first week of treatment depend on drug efficacy and can be used as an early predictor of longer-term response to ARV therapy.

Three PI naïve cohorts on different regimens were studied, taking measurements of CD4s (flow cytometry), VL (Amplicor) and baseline HIV-1 RNA concentrations. The "least squares" approach was used for data fitting to the model using the programme "Scientist", and for prediction, logistic regression analysis (Statistica 4.5) was used. The results indicated that there was no significant difference in baseline concentrations between the groups on mono-therapy and those on HAART ($p>0.21$) and that all HAART patients were good responders. The best predictions were obtained from multiple time-points during the first six days of therapy. The model may not accurately predict longer-term response in regimens in which resistance can develop very quickly (NNRTI mono-therapy), but it can be used for patients with drug-resistant mutants at entry. A larger cohort would need to be tested, along with cohorts of drug-experienced patients.

2.) Van der Groen G.: **The urgent need for feasibility studies of anti-retroviral treatment in HIV-infected individuals in resource-limited settings.** AIDS 2001 Nov 23; Vol. 15(17):2342-4.

In cognisance of the large majority of HIV-infected patients being unable to afford treatment, and the concomitant burden this places on governments of poor countries, this study examines the implications of the availability of cheap drugs, the increased demand and pressure this would impose on health services, and the follow-up infrastructure required to support such services.

The author examines arguments in favour of resistance monitoring in ART in developing countries, such as improvement in short-term virological outcome aiding in patient management, and cost-effectiveness being achieved through obviating hospitalisation and savings arising from the introduction of a drug holiday while waiting for resistance test results. He also points out that Phenotyping is expensive and time-consuming; Genotypic Antiretroviral Resistance Testing (GART) is faster, cheaper and less complex to perform, but more studies are needed to prove long-term clinical and viral load benefits. Virtual Phenotyping (the utility of raw genotypic resistance data in correlation with a phenotypic resistance database) allows the actual phenotype to be predicted with >90% accuracy, greater speed and lower costs.

Van der Groen emphasises the need for certified regional laboratories with strict quality assurance standards, equipped with a quality-controlled sequencing service; these facilities would use *pol* sequence data to identify genotypic resistance patterns as well as provide sub-type or inter-subtype-recombinant identification, the results of which could aid in vaccine design. He concludes that there is a need to protect the future utilisation of drugs by minimising the emergence of drug resistance, and that this factor should be incorporated into the budgets of international donor organisations supporting ART programmes in poor countries. Donors should also collaborate with each other so as to allocate larger budgets and thereby ensure sustained support, with feasibility studies of the use of limited ART, including resistance monitoring, being part of such sustained support.

Looking at recent advances in anti-retroviral therapy, Professor Cassol referred to three papers published in the March 2002 edition of The Lancet, and presented on one in particular, *viz*:

McCarthy M.: **New HIV drugs show promise in early studies**. The Lancet 2002 March 2; 359(9308):767.

In this paper presented at the 9th Annual Conference on Retro-viruses and Opportunistic Infections, Seattle, WA in February 2002, it is noted that the use of two major classes of anti-retroviral therapy (RTIs and PIs) has proved to be very successful in industrialised countries. In Africa, however, the

second class of drugs has not been as favourable, as they interact adversely with TB drugs. In high-income countries, HAART has transformed the course of HIV/AIDS into a chronic, treatable disease with decreased mortality and opportunistic infection, reversal of immune deficiency, reduced sexual transmission, reduced mother-to-child transmission and reduced hospitalisation.

The goals of anti-retroviral therapy are maximal, sustained suppression of HIV-1 replication below limits of detection in three to four months, and improved immunological function (indicated by 100 – 200 cells rise in CD4 count within the first year). Treatment failure would be constituted by insufficient viral suppression after four to six months with a return above 400 copies of viral/mL.

The article cites the two major classes of drugs available as well as their sub-groups and brand-names. Resistance mutations are present before therapy and are selected for:

- the chance of developing a virus with a single mutation being high
- the probability of developing mutations at two different positions in the same genome being less likely, and
- mutations at three different positions being even less likely, as the mutated virus would replicate less efficiently and be crippled.

The article then describes entry inhibitors, integrase inhibitors and alternative NNRTIs, concluding that one of the latter, namely **TMC 125**, is a new compound with unique properties, involving a highly flexible molecule that is effective when given to patients who are resistant to other standard NNRTIs such as Nevirapine, Efavirenz and Delavirdine. In two studies conducted using TMC 125, the single drug proved to be as effective as a five-drug combination and to have excellent penetration into the lymphatic tissues.

Professor Cassol recommended two further articles in the March 2002 edition of The Lancet (Vol. 359), namely:

Individualising HIV treatment: pharmacogenetics and immunogenetics, pages 722 – 3

and

Response to anti-retroviral treatment in HIV-1-infected individuals with alleleic variants of the multi-drug resistance transporter 1: a pharmacogenetics study pages 30 - 36

Report by Judith King, HIVAN Media Office