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## **CROI: Large cohorts show excellent responses to ART in developing countries**

**Derek Thaczuk & Virginia Differding**, Thursday, February 07, 2008

The positive impacts of antiretroviral programmes in several African countries and other resource-poor areas were highlighted in a series of oral presentations to the Fifteenth Conference on Retroviruses and Opportunistic Infections in Boston on Wednesday. These studies, which represent some of the first longer-term data on treatment response in low-income countries, pointed toward successes in patient retention, immune recovery, and reductions in mortality.

### **The National ART Program in Rwanda**

Encouraging results from nearly 3,500 patients enrolled in Rwanda's national ART programme were reported by Francois Ndamage of Rwanda's Ministry of Health. In its first two years of rapid scale-up, this programme achieved excellent immunologic outcomes and patient retention at six and twelve months.

An estimated 150,000 adult Rwandans (approximately 3% of the adult population) are HIV-positive. The national ART programme was established in 2004. By December 2007, over 47,000 persons had begun treatment at 83 sites – an impressive 68% of the estimated 69,000 Rwandans in need of ART

The data presented at CROI were the results of a retrospective cohort study: patients who had initiated ART in the period from January 2004 to December 2005 were randomly selected for this analysis. The sample was drawn from 30 clinic sites, and stratified by clinic size so as to be nationally representative. Demographic information and six-month and twelve-month clinical information was collected from the medical records of 3194 adults and 288 paediatric patients. For the adults, median age at ART initiation was 37 years, 65% were women, and the median CD4 cell count was 141 cells/mm<sup>3</sup>. The children ranged up to fourteen years of age with a median of seven years; most (71%) were between six and fourteen years old, and 50% were female.

Most first-line regimens consisted of 3TC (lamivudine), d4T (stavudine); 79% in adults and 84% in children) or AZT (zidovudine; 21% and 16%) and nevirapine (78% in adults and 74% in children) or efavirenz (22% and 26%).

### **Rwandan outcomes**

Most ART recipients (2,777 or 87% of the adults, and 261 or 91% of the children) were still receiving their therapy at twelve months.

For adult patients with follow-up data, median CD4 cell counts had increased by 98 cells/mm<sup>3</sup> at 6 months (n = 1445) and 119 cells/mm<sup>3</sup> at 12 months (n = 957). Larger increases in CD4 cells ( $\geq 120$  cells/mm<sup>3</sup>) were less likely in adults at large clinics (those with more than 1500 patients: OR 0.56; 95% confidence interval [CI], 0.38 to 0.82; p = 0.013) and medium-sized clinics (those with 75 to 1500 patients: OR 0.73; 95% CI, 0.56 to 0.95; p = 0.017) than in adults at small clinics (those with less than 75 patients). Patients (excluding pregnant women) gained a median of slightly more than three kg.

Children who were older when they started ART had lower mortality at six months (OR 0.60/year; p = 0.006) and at twelve months on treatment (OR 0.56/year; p = 0.005).

Overall, the evaluation of Rwanda's national ART programme showed excellent patient retention and substantial CD4 cell increases in both adults and children after one year of treatment. The study was limited by being retrospective and by incomplete follow-up data; the programme investigators hope to be able to conduct routine, representative sampling to continue to evaluate programme quality and patient outcomes.

### **A government ART Programme in rural KwaZulu Natal**

The HIV epidemic in KwaZulu Natal, South Africa, is particularly severe. Incidence rates are high, and prevalence rates vary widely by area but are estimated at 21% and exceed 35% in some areas. An estimated total of 1.5 million persons are infected. Graham Cooke reported, on behalf of a South African / UK study team, on significant declines in mortality in a rural area of KwaZulu Natal, South Africa – particularly in the 25-to-49 age group – following the roll-out of an ART programme in late 2004.

This study used data from demographic surveillance (from 2000) and from separate HIV surveillance (from 2003) in the Hlabisa sub-district of KwaZulu Natal. Data is collected and managed by the Africa Centre Demographic Information System (ACDIS), begun in 2000, which bi-annually collects birth, death, and migration data from roughly 65,000 residents in 11,000 households.

By the end of 2006, roughly 11% of HIV-positive people were accessing treatment in KwaZulu Natal. The main objective of the present study was to assess the impact of ART access, based on age-standardised mortality rates.

### **KwaZulu Natal outcomes**

Over 234,740 person-years of observation between January 2003 and December 2006, there were 3593 deaths. Between the first half of 2003 (before ART was introduced), to the second half of 2006, there were declines in death rates from all causes, and from deaths specifically due to HIV and tuberculosis (TB), in men and in women. Deaths due to HIV and tuberculosis fell from 22.3 per 1000 person-year in women and 23.1 in men in 2003/2004 (pre-ART), to 15.5 in women and 17.7 in men in 2005/2006.

Differences were most pronounced in the 25-to-49 age group, in whom the all-cause mortality rate fell from 28.9 deaths per 1000 person-year in women and 37.3 in men in 2003/2004, to 22.7 in women and 29.8 in men in 2005/2006. This represents a 22% drop in women (95% CI, 12% to 31%,  $p < .00001$ ) and a 20% drop in men (95% CI, 10% to 30%,  $p = .0002$ ).

In summary, a significant decline was seen in overall adult mortality within two years of an ART programme roll-out in a high-prevalence community, even with coverage rates of only roughly 11% - a "clear public health message" to encourage treatment access for all in need. There was a somewhat lesser impact on men's mortality rates, the reasons for which still need to be fully explored.

### **The ART-LINC Collaboration**

Denis Nash of the International Center for AIDS Care and Treatment Programs (ICAP) presented data from a meta-analysis of clinical information gathered from multiple HIV treatment sites in (mostly sub-Saharan) Africa, South America, and Southeast Asia. These data, drawn from a review of over 15,000 patient charts, showed a successful and durable CD4 response to ART in patients from these resource-limited settings.

Information was gathered from the pooled data of cohorts participating in the ART-LINC (Antiretroviral Therapy in Low Income Countries) Collaboration of the International Epidemiologic Databases to Evaluate AIDS (IeDEA). This research consortium was created to find answers to current and evolving treatment issues specific to patients in under-resourced areas.

The analysis included data from the records of treatment-naïve adults and adolescents who initiated ART in 1995, and for whom there was at least 6 months of follow-up information including at least two CD4 counts, documented between 31 days prior to and 5 years after the time ART was initiated. From an initial pool of 35,010 potential participants, 15,043 were ineligible or excluded due to insufficient data or baseline CD4 cell counts  $> 500$  cells/mm<sup>3</sup>. This left a final study population of 19,967 patients, corresponding to 39,200 person-years and 71,067 CD4 measurements. The median age was 35, median baseline CD4 count 114 cells/mm<sup>3</sup>, and 60% of the patients were women. Patients whose baseline CD4 counts were missing were not excluded, and in fact made up 21% of the sample.

### **ART-LINC outcomes**

Crude analysis showed a sizeable, continued rise in median CD4 count with increasing time on ART: from the baseline count of 114 cells/mm<sup>3</sup>, the median count was 230 cells/mm<sup>3</sup> at six months, 263 cells/mm<sup>3</sup> at twelve

months, 336 cells/mm<sup>3</sup> at 24 months, 377 cells/mm<sup>3</sup> at 48 months, and 395 cells/mm<sup>3</sup> at 60 months (although patient numbers declined with time).

By multivariate analysis, the factors with the greatest effect on the rate of CD4 cell count changes were baseline CD4 count, age, gender, and clinical site. Those with lower baseline CD4 counts eventually had a larger absolute change over time, but spent a longer time at levels <200 cells/mm<sup>3</sup>. Younger patients had higher counts than older patients; women had higher counts than men throughout the follow-up period and tended to have slightly greater increases. CD4 cell count responses also varied according to site.

This study was limited to sites with the ability to collect basic data electronically to contribute to ART-LINC. Also, patients could only be included if they had data from two or more CD4 counts, including one at or around the time of ART initiation. However, this study showed an excellent CD4 response to ART in a very large group of patients from multiple sites in resource-limited settings, and showed that this response could be sustained as long as five years. The researchers concluded that their observations were "encouraging for the sustainability of ART care in resource-limited settings for patients who access and remain on ART."

## References

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