

COHERE age project: Summary 11th October 2006

Aim: To investigate whether response to first-line ART is comparable across all age groups including babies, children, adolescents and older age groups.

Methods: All individuals from the participating cohorts and cohort collaborations who were previously antiretroviral naïve (not including MTC prophylaxis) were considered. Individuals starting combination antiretroviral therapy (cART; at least 3 drugs within 14 days) and with a CD4 count and viral load (VL) measured in the 6-month period before cART were included. Participants were also required to have at least one CD4 and at least one VL measurement after starting cART. A comparison of the characteristics of patients included and excluded from the study is shown in Table 1. Individuals were categorised according to their age when starting cART:

- <2 years (n=223 [0.5%])
- 2 to 5 years (n=184 [0.4%])
- 6 to 12 years (n=219 [0.4%])
- 13 to 17 years (n=201 [0.4%])
- 18 to 29 years (n=9134 [18.3%])
- 30 to 39 years (n=22410 [44.9%])
- 40 to 49 years (n=11588 [23.2%])
- 50 to 54 years (n=2693 [5.4%])
- 55 to 59 years (n=1656 [3.3%])
- 60+ years (n=1613 [3.2%])

Patient characteristics: These are described in Table 2. Participants' ages ranged from 1 day to 87 years. As expected, pre-cART CD4s varied according to age, the median in those aged <2 years being 1168 cells/mm³, dropping to 496 cells/mm³ in those aged 2-5, and 225 cells/mm³ in those aged 6 to 12. This then remained relatively constant across ages from 13 to 39 (222 cells/mm³ in 13-17 years, 256 cells/mm³ in 18-29 years, 210 cells/mm³ in 30-39 years), before steadily decreasing to 173 cells/mm³ in those aged 60+ years. Pre-cART VLs also varied by age: the median value was high amongst babies and small children (5.6 log copies/ml for <2 years; 5.2 log copies/ml for 2-5 years), and then remained at around 5 log copies/ml for older participants.

Treatment discontinuations: Results regarding time to discontinuing or substituting the first antiretroviral in the regimen are shown in Figure 3 and Tables 4 and 5. Rates of discontinuation were similar for those aged 13 years and older, but younger children were less likely to make changes to their regimen (Figure 3). By 12 months (Table 4), 34.2% of those aged <2 years had made a treatment change, compared to 26.0% of those aged 2 to 5 years, 27.4% of those 6 to 12 years, and approximately 47% for those in older age groups.

Time to discontinuation of all ART for at least 2 weeks is shown in Figure 6 and Tables 7 and 8. The percentage discontinuing cART within 12 months (Table 7) was low amongst those aged 0 to 12 years (7.9% of those <2 years, 6.2% of 2 to 5 years, 6.7% of 6 to 12 years) higher for those aged 13 to 39 years (15.3% 13 to 17 years, 14.8% 18 to 29 years, 11.4% 30 to 39 years), and again lower for those aged older than 40 at around 8% for all groups. The association with age continued even after adjusting for potential confounders (Table 8). Compared to those aged 30 to 39, there was a trend towards those aged 6 to 12 years being less likely to discontinue all ART (hazard ratio [HR]=0.81;

95% CI 0.59, 1.12; $p=0.20$). Those aged 13 to 29 were more likely to discontinue treatment (HR=1.31; 0.99, 1.73; $p=0.06$ for those aged 13 to 18 years: HR=1.11; 1.06, 1.17; $p<0.0001$ for 18 to 29 years). Older participants were less likely to discontinue all ART (HR=0.83; 0.79, 0.87 for 40 to 49 years; HR=0.71; 0.64, 0.78; 0.74 for 50 to 54 years; 0.66, 0.83 for 55 to 59 years; 0.73, 0.64, 0.82 for 60+ years; all $p<0.0001$).

Virological response: Prior to carrying out analyses we chose time to 2 consecutive VLs<50 copies/ml as the primary virological endpoint (Figure 15, Tables 16 and 17). Using this definition, the lowest percentages achieving a virological response was seen in those aged <2 years (34.0% by 12 months; Table 16). Responses then improved for those aged 2 to 5 years (40.2%) and 6 to 12 years (56.3%), before falling again for adolescents (45.6% for 13 to 17 years), and rose thereafter, reaching 61.8% achieving a response by 12 months for the 60+ age group.

Adjusting for potential confounders (Table 17), it can be seen that, compared to the 30 to 39 years group, younger individuals were less likely to experience a response (HR=0.87; 0.74, 1.02; $p=0.09$ 6 to 12 years; HR=0.78; 0.65, 0.94; $p=0.01$ for 13 to 17 years; HR=0.90; 0.88, 0.93; $p<0.0001$ for 18 to 29 years), and older individuals were more likely to experience a virological response (HR=1.10; 1.07, 1.13 for 40 to 49; HR=1.24; 1.19, 1.30 for 50 to 54 years; 1.24; 1.17, 1.32 for 55 to 59 years; 1.18; 1.12, 1.26 for 60+ years; all $p<0.0001$).

We carried out a number of sensitivity analyses. We considered defining virological response as a single VL<50 copies/ml (Figures 9-11), as a single VL<400 copies/ml (Figure 12-14), and as two consecutive VLs<400 copies/ml (Figures 18-20). We also restricted our primary virological endpoint to those starting cART from 2000 onwards to allow for the introduction of assays with lower limits of detection of 50 copies/ml at later time periods (Figure 15(a), Tables 16(a), 17(a)). We also considered VL at a specific time point, in case there were differences in the frequency of VL measurements in different age groups (Table 21; although we did not observe different frequency of monitoring). Although the results of these various analyses were broadly similar for older patients, there was evidence when using a <400 cut-off that those aged 6 to 12 years and 13 to 17 years had a comparable VL response to those aged 30 to 39 years.

Immunological response: Prior to carrying out analyses we chose time to 2 consecutive CD4s more than 100 cells/mm³ higher than pre-cART values as the primary immunological endpoint (Figure 25, Tables 26 and 27). The percent achieving an immunological response was highest in children (71.8% of those <2 years had had a response by 12 months, 82.2% of those aged 2 to 5, and 78.0% of those aged 6 to 12), and lower in adults and adolescents, at around 60.0% for all age groups. After adjustment for other potential confounders (Table 27), compared to those aged 30 to 49 years, the 6 to 12 years group had a better chance of response (HR=1.61; 1.39, 1.88; $p<0.0001$) and those aged 60+ had less chance of an immunological response (HR=0.93; 0.87, 0.98; $p=0.01$), but there was no clear pattern across other age groups.

Clinical progression: Time to the first new AIDS event or death is shown in Figure 29 and Tables 30 and 31. By 12 months (Table 30), the highest percentages of clinical progression were seen in young babies (12.4% for <2 years). The percentages then dropped until the 13 to 17 years group (4.8% by 12 months), before rising again, reaching 11.7% in the 60+ years group. After adjustment (Table 31) a similar response pattern was observed.