Research Highlights

Highlights from the latest articles in pediatric HIV

Antiretroviral treatment in HIV-infected African infants

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Evaluation of: Prendergast A, Mphatswe W, Tudor-Williams G *et al.*: Early virological suppression with three-class antiretroviral therapy in HIV-infected African infants. *AIDS* 22, 1333–1343 (2008).

Mother-to-child transmission of HIV is the most common route of infection for children, occurring during pregnancy, delivery or postnatally through breastfeeding [1]. However, transmission can be avoided to a substantial degree through the use of antiretroviral drugs given to the pregnant mother and to the infant shortly after delivery [2,3]. Prevention of mother-to-child transmission (PMTCT) programs are rolled out across the world, including the areas of sub-Saharan Africa that face the highest HIV burden [101]. The simplest and currently most widely used PMTCT approach uses single-dose nevirapine (sdNVP) given to the mother during labor and to the infant shortly after delivery. In addition, antiretroviral treatment (ART) programs for eligible HIV-infected people are also being rolled out across the continent. However, uncertainty remains not only about the optimum timing of initiation of ART in children, but also about the efficacy of currently available drug regimens in infants infected despite their exposure to sdNVP as PMTCT prophylaxis.

Prendergast and colleagues carried out a small study in two hospitals near Durban, South Africa to investigate the efficacy of infant ART in a setting where PMTCT was delivered as sdNVP. The study was a pilot, randomized trial to evaluate three approaches to ART in infants: deferred ART, started once clinical or immunological criteria were reached (arm A), immediate ART given for 1 year and then stopped (arm B), or immediate ART with up to three structured treatment interruptions to 18 months of age [4]. The analysis presented here considers as outcome virological suppression on treatment, combining arm B and C. A total of 63 infants with a diagnosis of intra-uterine or intra-partum HIV before 28 days of age were randomized to deferred (n = 20 in arm A) or immediate (n = 43 in arms B and C) ART. Some children died before the start of ART, and some died while on ART and before 1 year of follow-up, which left 49 infants who commenced ART in infancy and were followed-up for 1 year or more. All infants were infected with HIV clade C; genotypic resistance to the class of drugs sdNVP belongs to was identified in 20 of 51 (39%) infants tested. Treatment adherence in the children was high (95–99%).

The first-line regimen was a combination of four ART drugs (ziodvudine, lamivudine, nelfinavir and nevirapine – the latter was discontinued once RNA viral load was below 50 copies per ml). Age at initiation of ART in the deferred group was a median of 142 days (range: 81–227 days), 1–106 days after eligibility criteria were met. In the immediate group, ART was started on median day 28 (range: 8–164 days) in infants with evidence of intra-uterine infection and day 55 (range: 36–90 days) in infants with intra-partum/early breastfeeding infection. RNA viral load 1 year post-ART initiation was less than 400 copies per ml in all children, and less than 50 copies per ml in 92% of the deferred ART group, and 94% in the immediate group. Median time to viral load below 50 copies was 121 days (range: 15–308 days) in the immediate and 115 days (range: 76–204 days) in the deferred group; time to viral suppression did not differ statistically significantly between the groups.

This study provides evidence that ART can be highly successful in vertically

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acquired HIV infection, but the number of infants evaluated was small and the study thus suffered from lack of statistical power. Further follow-up is ongoing, and the medium-term outcomes regarding the cessation or structured interruption of ART in these infants is awaited. However, the findings confirm results emerging from other settings and highlight the need to expand both PMTCT and pediatric ART services in resource-poor settings.

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Does antiretroviral therapy provide continuous improvement in immune system function in HIV-infected children?

Evaluation of: Weinberg A, Dickover R, Britto P *et al.*: Continuous improvement in the immune system of HIV-infected children on prolonged antiretroviral therapy. *AIDS* 22, 2267–2277 (2008).

A further concern expressed in the discussion regarding the optimum timing of initiation of ART in vertically infected children regards the balance of potential side effects associated with ART, and whether or not the increase in the number of CD4 cells with duration of ART is associated with improved functionality of the immune system. It has been previously recognized that HIV infection alters the distribution of T-cell phenotypes, but there is little evidence as to whether ART reverses this pattern. Weinberg and colleagues addressed this question using samples collected from children enrolled in the PACTG 1021. The study enrolled 37 HIV-infected children in the USA, between the ages of 3 and 21 years, as two cohorts: those 3–12 years old (n = 21) and adolescents 13–21 years of age (n = 16); all had acquired HIV vertically. The children were either ART-naive or had had limited previous exposure to ART as perinatal PMTCT or as less than 7 days cumulative ART. They were required to have RNA plasma viral load of at least 5000 copies per ml at study entry. The highly active antiretroviral therapy (HAART) regimen consisted of emtricitabine, didanosine and efavirenz once daily. Immunological assays were performed at weeks 0, 24, 48, 144 or end of study if different from 144 weeks.

Over the 3 years of follow-up following HAART initiation, plasma RNA rapidly decreased and became undetectable in 81% of children at week 24 and 77% at 144 weeks. CD4% at baseline was inversely correlated with plasma HIV RNA, but not at subsequent time points – presumably because RNA viral load became undetectable. CD4% increased with duration of treatment; this increase was greater for children with higher CD4% at baseline than for those with lower baseline percentage. The studies of the T-cell phenotypic distribution showed that naïve CD4% increased during the first 48 weeks on HAART and remained stable thereafter. Memory CD4% and activated CD4% decreased during the first 48 weeks of treatment, but not thereafter. By contrast, CD8 T cells and subpopulations were continuously remodeled during the entire 144 weeks of observation. There were no appreciable differences between the two age cohorts with respect to changes in CD4 T-cell subpopulations or phenotypic changes in CD8 T cells in response to HAART. During the first year of ART, a higher percentage of activated CD4 cells was significantly associated with immune dysfunction, including lower CD4%.

This study provides evidence that HIV-infected children undergo progressive immune reconstruction in response to HAART, which could potentially lead to normalization of immune parameters. The study extents previous observations by showing that not only CD4 T cells, but also functional and phenotypic immune measures, continue to improve in HIV-infected children over 3 years of effective HAART. This study demonstrates complete normalization of T-cell subpopulations, including naïve and activated CD4 and naïve CD8 cells. The active and total CD8 cells remained elevated, possibly due to low-level viremia; further normalization after 3 years of treatment could be possible. Results also suggest that it is most likely that the reconstitution of T cells and their subpopulations derived from the large thymic reserve seen at young ages. This would be a further argument for earlier rather than later initiation of HIV treatment in children with vertically acquired HIV.

Impact of genetic variants in chemokine receptors on the risk of mother-to-child transmission of HIV

Evaluation of: Singh KK, Hughes MD, Chen J: Associations of chemokine receptor polymorphisms with HIV-1 mother-to-child transmission in sub-Saharan Africa: possible modulation of genetic effects by antiretrovirals. *J. AIDS* 49(3), 259–265 (2008).

Prevention of mother-to-child transmission (PMTCT) programs are being scaled-up in resource-limited areas of the world; however, what drives mother-to-child transmission, and why some women with low viral loads transmit HIV to their infants, whilst other women with high viral loads do not transmit, remain largely unanswered questions. Singh *et al.* examined the impact of genetic variants in chemokine and chemokine receptors [1], including the co-receptor CCR5 variants, on the risk of mother-to-child transmission of HIV, and the effect that short-course antiretroviral drugs, given to women as part of PMTCT programs, had on host genetics.

A total of 980 mother–infant pairs were included from vitamin A trials in Malawi [2] (n = 322, antiretroviral [ARV]-naive) and South Africa [3] (n = 300, ARV-naive), and from the 012 trial in Uganda [4] (n = 358, most women had been treated with either single-dose nevirapine or perinatal zidovudine, with 15 ARV-naive). The HIV status of infants at 6 weeks of age was determined using real-time PCR.

The proportion of HIV-infected infants from the three studies, and maternal HIV-RNA levels at delivery, were not significantly different between the sites; maternal median CD4 count at delivery was lower in the Malawian women (399 cells/µl) compared with those from South Africa (440 cells/µl) and Uganda (447 cells/µl); p = 0.049. Genotypes studied included *CCR5* promoter, *CCR2* and *CX_3CR1*.

An association with perinatal HIV transmission was found between the *CCR5* promoter variants at positions 59029 and 59353. ARV-naïve infants with the *CCR5*-59029-A allele had a higher risk of mother-to-child transmission than those with the G/G allele (odds ratio [OR]: 1.61; 95% confidence interval [CI]: 1.04–02.48, p = 0.032); however, interestingly, infants with the A allele who had been exposed to nevirapine were less likely to be infected, whereas those exposed to zidovudine were more likely to be infected. The authors suggest that the long half-life and rapid decline in viral load associated with nevirapine accounted for this difference. Similar results were found in infants with the *CCR5*-59353 variants.

For infants with the variant *CX_3CR1*-745-A allele as opposed to the G genotype, there was no link with mother-to-child transmission in those who were ARV-naïve. However, those who had been exposed to nevirapine or zidovudine were at greater risk of acquiring HIV (nevirapine: OR: 5.64, 95% CI: 1.40–22.78; p = 0.015; zidovudine: OR: 5.02; 95% CI: 1.71–14.68, p = 0.003). There were no significant associations found for the *CCR2* variants.

Further research is needed to help unravel the complex interactions of chemokines and other host genetic factors on mother-to-child transmission of HIV, and the modifying effect short-course antiretrovirals may have on host genetics. However, the results of this study add to the growing body of literature which suggests that host genetics have an important role to play in mother-to-child transmission and may be modified by maternal antiretroviral therapy.

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