Neurodevelopment in Children Born to HIV-Infected Mothers by Infection and Treatment Status

abstract

BACKGROUND: We reviewed the impact of HIV, HIV exposure, and antiretroviral therapy/prophylaxis on neurodevelopmental outcomes of HIV-infected and HIV-exposed-uninfected infants and children.

METHODS: A literature search of Medline, Embase, PsychINFO, Web of Science, PubMed, and conference Web sites (1990–March 2011) using the search terms, infant, child, HIV, neurodevelopment, cognition, language, and antiretroviral therapy, identified 31 studies of HIV/antiretroviral exposure using standardized tools to evaluate infant/child development as the main outcome. Articles were included if results were reported in children <16 years of age who were exposed to HIV and antiretrovirals in fetal/early life, and excluded if children did not acquire HIV from their mothers or were not exposed to antiretrovirals in fetal/early life.

RESULTS: Infants who acquired HIV during fetal and early life tended to display poorer mean developmental scores than HIV-unexposed children. Mean motor and cognitive scores were consistently 1 to 2 SDs below the population mean. Mean scores improved if the infant received treatment before 12 weeks and/or a more complex antiretroviral regimen. Older HIV-infected children treated with highly active antiretroviral therapy demonstrated near normal global mean neurocognitive scores; subtle differences in language, memory, and behavior remained. HIV-exposed-uninfected children treated with antiretrovirals demonstrated subtle speech and language delay, although not universally.

CONCLUSIONS: In comparison with resource-rich settings, HIV-infected and HIV-exposed-uninfected infants/children in resource-poor settings demonstrated greater neurodevelopmental delay compared with HIV-unexposed infants. The effects on neurodevelopment in older HIV-infected children commenced on antiretroviral therapy from an early age and HIV-exposed-uninfected children particularly in resource-poor settings remain unclear. Pediatrics 2012;130:e1326–e1344

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KEY WORDS
neurodevelopment, HIV, childhood development, antiretroviral therapy, HAART

ABBREVIATIONS
ARV—antiretroviral drug
HAART—highly active antiretroviral therapy

Dr Le Doaré prepared and undertook the literature review and was responsible for writing the first draft of this article. Professor Newell and Dr Bland reviewed the data and provided comments during writing, and substantially contributed to, and approved, the final manuscript.

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Mother-to-child transmission during pregnancy, delivery, or breastfeeding is the dominant mode of acquisition of HIV infection in children. Without prophylaxis, ~15% to 30% of babies born to HIV-infected women will acquire HIV in utero or during delivery and a further 5% to 20% through breastfeeding. Maternal HIV has been associated with an increased risk of low birth weight (<2500 g) and small-for-gestational-age infants, both of which are independently associated with an increased risk of mortality and of developmental delay.

HIV-1 is thought to enter the central nervous system days to weeks after primary infection, causing neuronal damage and cell death. This infective process manifests in childhood as a progressive encephalopathy, and previously affected 8% to 50% of children diagnosed with HIV infection in the United States and Europe. Symptoms can vary greatly, with motor manifestations predominating. Microcephaly can be seen as a result of brain atrophy and radiologic studies demonstrate periventricular and basal ganglia calcifications and cerebral matter attenuation.

Studies of cerebrospinal fluid from children with progressive encephalopathy found active and persistent brain infection, highlighting the need for antiretroviral drugs (ARVs) that cross the blood-brain barrier. This information has recently been developed into a ranking system to aid clinicians’ ARV prescribing. Highly active antiretroviral therapy (HAART), containing ARVs that cross the blood-brain barrier, has been found to reduce the incidence of progressive encephalopathy by 50% compared with non-HAART regimens. With the routine use of ARVs in childhood in the United States and Europe, cumulative incidence of progressive encephalopathy in HIV-infected children aged 6 months to 16 years has fallen from more than 30% to less than 2%. Prevention of mother-to-child transmission through maternal ARV prophylaxis and treatment has successfully reduced transmission rates since the 1990s and in countries offering a combination of ARV prophylaxis, elective cesarean delivery, and avoidance of breastfeeding, transmission rates of <2% have been reported.

HAART has been associated with severe prematurity (twofold increased risk of being born at <32 weeks’ gestation) in Europe and the United States. Similar reports from Africa, where most women with HIV infection live, indicated that women on a HAART regimen containing a protease inhibitor were twice as likely to deliver prematurely (before 37 weeks) than those on a regimen not containing a protease inhibitor and were 50% more likely to deliver extremely premature infants (before 28 weeks). An increased risk has also been reported in regimen containing efavirenz and nevirapine. Severe prematurity increases the risk of cerebral events, such as hypoxic brain injury and cerebral hemorrhage, which will affect future neurodevelopmental potential.

Interventions to improve development in the first 3 years of life, including nutritional supplementation, developmental stimulation, dedicated health and community-based development centers, have demonstrated sustained improvement in later cognition and schooling in developing countries but this has not been specifically investigated in children affected by HIV.

Assessing neurodevelopmental outcomes is a difficult task owing to potential confounders, such as maternal health, mood, infant-mother bonding and attachment, early years stimulation, maternal substance misuse, poverty, illiteracy, malnutrition, and disease. The past 10 years have seen a large investment in prevention of mother-to-child transmission programs and the treatment of HIV-infected children at an earlier disease stage with more aggressive therapy. With earlier detection and improved treatment, HIV has become a chronic disease rather than a fatal illness. Therefore, improving the quality of life for infants and children affected by HIV, including interventions to improve neurodevelopmental outcomes and maximize school achievement are vital. This review aims to summarize what has been learned about neurodevelopmental outcomes in HIV-infected and HIV-exposed-uninfected infants and children and discusses the effects of different antiretroviral regimens on neurodevelopmental outcomes. We discuss the implications of these findings to improve the care of children infected and affected by HIV.

METHODS

We searched the online databases Medline, Embase, PsychINFO, Web of Science, and PubMed for studies published in English between 1990 and March 1, 2011, with the following search terms: “infant,” “child,” “HIV,” “neurodevelopment,” “cognitive impairment,” “motor impairment,” “language impairment,” “antiretroviral therapy.” The search identified 210 studies in Medline; subsequent searches identified additional studies: 16 in Embase, 7 in PsychINFO, and 12 in PubMed. The results of this review have been reported using the checklist described for writing systematic reviews by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The current focus of HIV programs globally is on prevention of mother-to-child transmission and early detection of childhood infection with immediate treatment. Therefore, to determine the effect on neurodevelopment of maternal
HIV and possible ARV exposure in utero or early life, and of childhood exposure to ARVs, studies were included if they met the following criteria:

1. The study concerned HIV-infected and HIV-exposed-uninfected infants and children <16 years of age who were exposed to ARVs in fetal and/or early life
2. The study used a standardized tool to evaluate infant/child development
3. A developmental variable was the main outcome
4. English language articles/abstracts

Studies of special groups, such as patients with hemophilia, orphans, or HIV-infected children who had not acquired HIV infection via mother-to-child transmission, were excluded, as these groups would either not have been exposed to HIV/ARVs in utero or have other potential confounders that are known to affect development, independent of child health status. In addition, a manual search of the references from selected articles and recent conferences of interest (international AIDS conferences, Conference on Retroviruses and Opportunistic Infections from 2002–2010) was carried out to ensure all relevant articles were identified. This yielded an additional 8 studies that met the inclusion criteria; 31 studies fulfilled the inclusion criteria and were reviewed (Fig 1).

CHARACTERISTICS OF STUDIES

Three-quarters of the studies reviewed (75%) emanated from the United States or Canada (n = 18) and Europe (n = 5), whereas studies from resource-poor settings accounted for 25%: Africa (n = 6), South/Central America and the Caribbean (n = 1), and Asia (n = 1). The characteristics of the studies included in this review are outlined in Tables 1, 2, and 3.

The prevalence of infants born before 37 weeks’ gestation ranged from 6% to 29% in HIV-infected children and 2.8% to 17.3% in HIV-exposed-uninfected children. The prevalence of low birth weight (<2500 g) among HIV-infected children ranged from 13% to 33% and 12% to 16% in HIV-exposed-uninfected children. Only 1 study commented on mean duration of ARVs in pregnancy (17.7 weeks).

Additional exposure to maternal alcohol and drug abuse, including cocaine, cannabis, and heroine was reported in 31 studies with a prevalence of between 9% and 67%. All these studies were from the United States or Europe.

HIV-INFECTED INFANTS AND CHILDREN EXPOSED TO ARVS IN RESOURCE-RICH SETTINGS

**HIV-Infected Infants**

HIV-infected infants examined using the Bayley Scales of Infant Development (I and II, Psychomotor Developmental Index, and Mental Developmental Index, mean score of 100, SD 15) displayed mean neurodevelopmental scores more than 1 SD below the population mean. Compared with HIV-exposed-uninfected infants, HIV-infected infants...
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<thead>
<tr>
<th>First Author</th>
<th>Year</th>
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<th>Developmental Outcomes</th>
<th>Additional Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nozce (45)</td>
<td>1994</td>
<td>US</td>
<td>Cohort</td>
<td>274</td>
<td>All HIV-infected</td>
<td>3–24 mo</td>
<td>BSID</td>
<td>Not antenatally. On therapy depending on disease stage. ARVs not stated.</td>
<td>Yes – not stated</td>
<td>Those with worse disease stage at higher risk of lower neurodevelopmental scores than the population mean.</td>
<td></td>
</tr>
<tr>
<td>Chase (46)</td>
<td>1995</td>
<td>US</td>
<td>Cohort</td>
<td>51</td>
<td>HIV-infected = 24 HIV-exposed-uninfected = 27</td>
<td>4–70 mo</td>
<td>BSID</td>
<td>Yes, not stated when ARVs not stated.</td>
<td>Not stated</td>
<td>Early motor delay and mental decline if HIV-infected versus HIV-exposed-uninfected. Mean scores decelerate over time. Variable outcomes, even if HIV-infected.</td>
<td></td>
</tr>
<tr>
<td>Pollack (44)</td>
<td>1996</td>
<td>US</td>
<td>Cohort</td>
<td>91</td>
<td>HIV-infected = 22 HIV-exposed-uninfected = 42 HIV-unexposed = 27</td>
<td>0-2 y</td>
<td>BSID</td>
<td>Not stated if antenatally. 11/18 zidovudine postnatally at mean age of 4.5 mo.</td>
<td>Yes – not stated</td>
<td>Mean MDI and PDI scores comparable at birth but declined versus controls by 12 mo if HIV-infected (83.5 vs 112 vs 116, ( P = .01 )). HIV-infected 10.5 times more likely to have mean MDI score &gt;1 SD lower and 4.4 times more likely PDI mean score &lt;85 (&lt;1 SD) below population mean.</td>
<td></td>
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<tr>
<td>Culnane (48)</td>
<td>1999</td>
<td>US and France</td>
<td>Cohort</td>
<td>332</td>
<td>HIV-exposed-uninfected</td>
<td>0–3 y</td>
<td>BSID MSCA</td>
<td>Not stated if antenatally. Infants received zidovudine</td>
<td>Not stated</td>
<td>No SDs in groups for BSID or MSCA.</td>
<td></td>
</tr>
<tr>
<td>Raskino (49)</td>
<td>1999</td>
<td>US</td>
<td>Cohort</td>
<td>831</td>
<td>All HIV-infected</td>
<td>2 mo–18 y</td>
<td>BSID, MSCA, WIT</td>
<td>Not stated if antenatally. Infants randomized to receive zidovudine or didanosine monotherapy or combination zidovudine and didanosine therapy</td>
<td>Yes - not stated</td>
<td>Developmental results improved with combination zidovudine and didanosine.</td>
<td></td>
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</table>

**TABLE 1 Infants Exposed to HIV/ARVs In Utero and Early Life in Resource-Rich Settings**
<table>
<thead>
<tr>
<th>First Author (Reference No.)</th>
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<tbody>
<tr>
<td>Chase (47)</td>
<td>2000</td>
<td>US</td>
<td>Cohort</td>
<td>595</td>
<td>HIV-infected = 114, HIV-exposed-uninfected = 481</td>
<td>0–36 mo</td>
<td>BSID</td>
<td>Yes, not stated when. ARVs not stated.</td>
<td>Yes – 38.7% to 55.8% in all mothers</td>
<td>HIV-infected RR of &gt;1 SD below population mean for neurodevelopment: 1.5 CI (1.03–2.18) ( P = .034 ); RR &gt;2 SDs below population mean for neurodevelopment: 2.40, 95% CI: 1.27–4.56, ( P = .007 ). RR of PDI &gt;1 SD below population mean: 1.66, CI (1.12–2.45) ( P = .01 ); RR &gt;2 SDs below population mean: 3.81, 95% CI: 1.93–7.54, ( P = .001 ).</td>
<td>Prematurity, maternal education assoc. with lower mean neurocognitive scores</td>
</tr>
<tr>
<td>Smith (50)</td>
<td>2000</td>
<td>US</td>
<td>Cohort</td>
<td>114</td>
<td>All HIV-infected</td>
<td>0–3 y</td>
<td>BSID</td>
<td>Not stated if antenatally. All infants treated with zidovudine.</td>
<td>Yes 48%</td>
<td>At 4 mo no significant difference except in mean scores. Mean score &lt;1 SD from the population mean by 24 mo for both MDI and PDI ( P &lt; .05 ). Early HIV-1 infection was associated with a decline in estimated mean motor scores of 1 standard score point per mo compared with 0.28 point in the late infected group ( P &lt; .02 ). Estimated mean mental scores of the early-infected group declined 0.72 point/mo, whereas the average decline of the late-infected group was 0.30 point/mo ( P &lt; .13 ).</td>
<td>Prematurity, birth weight*</td>
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<tr>
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<tr>
<td>Blanchette (51)</td>
<td>2001</td>
<td>Canada</td>
<td>Cross-sectional</td>
<td>50</td>
<td>HIV-infected = 25 HIV-exposed-uninfected = 25</td>
<td>6–37 mo</td>
<td>BSID</td>
<td>Not stated when.</td>
<td>Yes – 20% in HIV-infected mothers</td>
<td>Mean MDI lower in HIV-infected group ( P &lt; .001 ) ( [71.4 \text{ CI } 62.4–80.4] ) versus 92.3 ( [\text{CI } 84.5–99.9] ). Mean PDI lower in HIV-infected group ( [61.9 \text{ CI } 55.3–68.6] ) vs 90.9 ( [\text{CI } 80.1–98.1] ) ( P &lt; .001 ); HIV-exposed-uninfected normal scores in all domains.</td>
<td></td>
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<tr>
<td>Llorente (52)</td>
<td>2003</td>
<td>US</td>
<td>Cohort</td>
<td>157</td>
<td>All HIV infected</td>
<td>0–36 mo</td>
<td>BSID</td>
<td>Not stated if antenatally.</td>
<td>38% to 63%</td>
<td>Children with worse disease had scores &gt;2 SDs below the population mean. Increased risk of mortality per 10-point decrement in initial MDI and PDI scores versus population mean, even after adjusted for treatment. 1.32 ( [\text{CI } 1.07–1.63] ).</td>
<td></td>
</tr>
<tr>
<td>Foster (64)</td>
<td>2006</td>
<td>UK</td>
<td>Cohort</td>
<td>82</td>
<td>HIV-infected</td>
<td>7–33 mo</td>
<td>BSID, GMDI</td>
<td>Not stated if antenatally. Category C disease: all received ARVs; 12/31 mono/dual therapy before HAART, median number of drugs = 5 (range 3–12). Category A/B disease: 23/31 HAART, 9 received mono/dual therapy before HAART, Median number of drugs = 4 (range 2–11).</td>
<td>Not stated</td>
<td>Lower verbal scores than population mean. Children with worse disease stage have scores &gt;2 SDs below the population mean, not improved by HAART.</td>
<td></td>
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</table>

CT abnormalities – scores worse in HIV-infected if also had CT abnormalities.
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<tbody>
<tr>
<td>Alimenti (54)</td>
<td>2006</td>
<td>US</td>
<td>Cross-sectional</td>
<td>63</td>
<td>HIV-exposed-uninfected = 39 HIV-unexposed = 24</td>
<td>18–36 mo</td>
<td>BSID</td>
<td>All HAART exposed: at least 3 ARVs for at least 1 wk during pregnancy and zidovudine at delivery and postnatal period (mean 17.7 wk of exposure).</td>
<td>Yes — 51% HIV-exposed-uninfected versus 12% HIV-unexposed</td>
<td>Percentage MDI scores &gt;1 SD below the population mean 54% vs 25% P = .025; not significant when adjusted for maternal substance misuse.</td>
<td>Prematurity, low birth weight</td>
</tr>
<tr>
<td>Lindsey (55)</td>
<td>2007</td>
<td>US</td>
<td>Cohort</td>
<td>1211</td>
<td>HIV-infected = 152 HIV-exposed-uninfected = 1059</td>
<td>0–2 y</td>
<td>BSID</td>
<td>79% antenatally. Infants on HAART ± protease inhibitor</td>
<td>11% to 25%</td>
<td>In pre-protease inhibitor era, HIV-infected lower MDI and PDI versus HIV-exposed-uninfected by 1 y of age and remained lower at age 2 y. Limited improvement in MDI and PDI with addition of PI-based HAART.</td>
<td>Low birth weight, gestational age</td>
</tr>
<tr>
<td>Caplo (63)</td>
<td>2008</td>
<td>Italy</td>
<td>Cross-sectional</td>
<td>29</td>
<td>HIV-infected = 15 HIV-exposed-uninfected = 14</td>
<td>2 wk–36 mo</td>
<td>DDST</td>
<td>Yes, not stated when. ARVS not stated.</td>
<td>Excluded</td>
<td>HIV-infected infants 62.5% abnormal scores vs 14% if HIV-exposed-uninfected. Treatment before 12 wk of age improved scores versus those treated later.</td>
<td>Not stated</td>
</tr>
<tr>
<td>Williams (53)</td>
<td>2010</td>
<td>US</td>
<td>Cohort</td>
<td>1840</td>
<td>All HIV-exposed-uninfected</td>
<td>0–2 y</td>
<td>BSID</td>
<td>Yes — 184 exposed to any ARVs antenatally.</td>
<td>Yes -17% MDI 94.8 vs 92.2, PDI 93.9 = near normal. Improved MDI scores with increased duration of maternal therapy (92 for 0 wk versus 95.9 for &gt;26 wk exposure). MDI scores also improved with maternal zidovudine and lamivudine therapy in second and third trimesters.</td>
<td>Infants with low birth weight had better scores if ARV exposed.</td>
<td></td>
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</tbody>
</table>

BSID, Bayley Scales of Infant Development; CI, confidence interval; MDI, Mental Developmental Index; MSCA, McCarthy Scale of Childhood Abilities; PDI, Psychomotor Developmental Index; PI, protease inhibitor; RR, relative risk; WIT, Wechsler Intelligence Tests.

a Children followed until 5 y of age.
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<tr>
<td>Levenson (56)</td>
<td>1992</td>
<td>US</td>
<td>Cross-sectional</td>
<td>49</td>
<td>HIV-infected = 41, HIV-exposed-uninfected = 8</td>
<td>School-age</td>
<td>MSCA</td>
<td>Not stated when. ARVs not stated</td>
<td>Yes, not stated how many</td>
<td>44% scored &gt;2 SDs below the population mean. Poor verbal and memory scores if HIV-infected and symptomatic.</td>
<td>Not stated</td>
</tr>
<tr>
<td>Bisiacchi (62)</td>
<td>2000</td>
<td>Italy</td>
<td>Cross-sectional</td>
<td>42</td>
<td>HIV-infected = 29, HIV-exposed-uninfected = 13</td>
<td>6–15 y</td>
<td>Own tests</td>
<td>Not stated when. ARVs not stated</td>
<td>Not stated</td>
<td>Executive function scores lower in HIV-infected than HIV-exposed-uninfected; language and memory scores only poorer with worse disease. HIV-exposed scores normal for age</td>
<td>Not stated</td>
</tr>
<tr>
<td>Fishkin (57)</td>
<td>2000</td>
<td>US</td>
<td>Cross-sectional</td>
<td>80</td>
<td>HIV-infected = 40, HIV-unexposed = 40</td>
<td>3–5 y</td>
<td>WIT</td>
<td>Not stated when. ARVs not stated</td>
<td>Yes, not stated how many</td>
<td>All neurocognitive scores lower in HIV-infected group but not significant; only significant difference executive function: block design 6.08 vs 7.53 P = .002</td>
<td>Not stated</td>
</tr>
<tr>
<td>Blanchette (61)</td>
<td>2001</td>
<td>Canada</td>
<td>Cross-sectional</td>
<td>25</td>
<td>HIV-infected = 14, HIV-exposed-uninfected = 11</td>
<td>5–12 y</td>
<td>WIT</td>
<td>Not stated when. 4 children on ARVs + Pl 8 children ARVs without Pl. Average no. of drugs = 2 (range 0–4)</td>
<td>Yes – 20% in HIV-infected mothers</td>
<td>No differences in cognition. Subtle fine and gross motor strength differences. Significant differences in mean scores in HIV-infected with worse disease stage. CT changes associated with visuospatial and visuomotor difficulties.</td>
<td>Not stated</td>
</tr>
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<tr>
<td>Jeremy (59)</td>
<td>2005</td>
<td>US</td>
<td>Cohort</td>
<td>489</td>
<td>All HIV-infected</td>
<td>24 mo–17 y</td>
<td>BSID</td>
<td>Postnatally owing to infection, not stated if antenatally</td>
<td>Mean age 6.8 y Postnatal: zidovudine/lamivudine (100), stavudine/ritonavir (97), zidovudine/lamivudine/ritonavir (100). Pre-1997: zidovudine/lamivudine (100), stavudine/ritonavir (97), zidovudine/lamivudine/ritonavir (100).</td>
<td>Yes, not stated</td>
<td>Motor, memory, and language scores &gt;1 SD below the population mean at baseline. Small improvement in verbal score only with introduction of PI-based ARVs, no difference between the PI-containing regimen.</td>
</tr>
<tr>
<td>Smith (60)</td>
<td>2006</td>
<td>US</td>
<td>Cohort</td>
<td>539</td>
<td>HIV-infected = 117</td>
<td>3–7 y</td>
<td>MSCA</td>
<td>Not stated if antenatally</td>
<td>HIV-exposed-uninfected = 422</td>
<td>Only children with the class C disease performed poorly. All other scores comparable with norms.</td>
<td>Yes – 41%</td>
</tr>
<tr>
<td>First Author (Reference No.)</td>
<td>Year</td>
<td>Location</td>
<td>Study Type</td>
<td>n</td>
<td>Groups Studied</td>
<td>Age at Entry</td>
<td>Development Scale</td>
<td>Exposure to ARVs</td>
<td>Additional In Utero Exposure to Drugs (Cocaine, Heroin, Other)</td>
<td>Developmental Outcomes</td>
<td>Developmental Measures</td>
</tr>
<tr>
<td>-----------------------------</td>
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</tr>
<tr>
<td>Koekkoek (65)</td>
<td>2008</td>
<td>Netherlands</td>
<td>Cohort</td>
<td>22</td>
<td>All HIV-infected</td>
<td>6–17 y</td>
<td>SON</td>
<td>18 postnatally treated with HAART. Not stated antenatally</td>
<td>Global scores within the average range. Differences in executive function noted with mean scores &gt;1 SD below the population mean in: verbal scores, baseline speed, pattern recognition, shifting set, visuospatial memory all P &lt; .001.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brackis-Cott (58)</td>
<td>2009</td>
<td>US</td>
<td>Cross-sectional</td>
<td>325</td>
<td>HIV-infected = 206</td>
<td>9–16 y</td>
<td>PPVT, WRAT III</td>
<td>Not stated if antenatal exposure.</td>
<td>33% HIV-infected scored below 10th centile in both tests. PPVT/HIV-infected mean score 83.9 vs 85.3. HIV-exposed-uninfected: mean score 87.5</td>
<td>Youths on ARVS had lower WRAT III scores than those not taking medication</td>
<td></td>
</tr>
<tr>
<td>Thomaidis (66)</td>
<td>2010</td>
<td>Greece</td>
<td>Cross-sectional</td>
<td>60</td>
<td>HIV-infected = 20 HIV-unexposed = 40</td>
<td>3–18 y Mean age 11.76 y</td>
<td>WIT, GMDI</td>
<td>All HIV-infected treated with HAART not stated when treatment started. Not stated if antenatal</td>
<td>HIV-infected with CT changes had lower mean general, practical and IQ scores P &lt; .001. HIV-infected without CT abnormalities had normal cognitive scores but increased emotional symptoms and hyperactivity P &lt; .05.</td>
<td></td>
<td>Prematurity and low birth weight</td>
</tr>
</tbody>
</table>

BSID, Bayley Scales of Infant Development; CI, confidence interval; CT, computed tomography; GMDI, Griffiths Mental Developmental Index; MDI, Mental Developmental Index; MSCA, McCarthy Scale of Childhood Abilities; PI, protease inhibitor; PPVT, Peabody Picture Vocabulary Test; SON, Snijers-Oomen Non-verbal WIT; Wechsler Intelligence Tests; WRAT, Wide-Ranging Ability Test.
<table>
<thead>
<tr>
<th>Author Year</th>
<th>Location Study Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gay (73) 1995 Haiti Cohort</td>
<td>126 HIV-infected = 28 HIV-exposed-uninfected = 98</td>
</tr>
<tr>
<td>Smith (71) 2008 South Africa Cohort</td>
<td>39 HIV-infected</td>
</tr>
<tr>
<td>Van Rie (72) 2008 Congo Cross-sectional</td>
<td>160 HIV-infected = 35 HIV-exposed-uninfected = 35 HIV-unexposed=90</td>
</tr>
<tr>
<td>Leartvanangkui (74) 2008 Thailand Cross-sectional</td>
<td>304 HIV-infected = 25 HIV-exposed-uninfected = 279</td>
</tr>
</tbody>
</table>

**TABLE 3** Infants and Children Exposed to HIV/ARVs in Resource-Poor Settings

<table>
<thead>
<tr>
<th>n</th>
<th>Groups Studied</th>
<th>Age at Entry</th>
<th>Development Scale</th>
<th>Exposure to ARVs</th>
<th>Exposure to Drugs (Cocaine, Heroin, Other)</th>
<th>Additional In Utero Exposure to Drugs</th>
<th>Developmental Outcomes</th>
<th>Additional Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gay (73) 1995 Haiti Cohort</td>
<td>126 HIV-infected = 28 HIV-exposed-uninfected = 98</td>
<td>0–24 mo</td>
<td>BSID</td>
<td>Not in utero, 13 infants treated with zidovudine, mean age at initiation 14.6 mo</td>
<td>No</td>
<td>Mean MDI and PDI scores &gt; 1 SD below the population mean if HIV-infected at 3 mo. Differences between groups increased over time. 33% normal cognitive scores, 50% normal motor scores.</td>
<td>Not stated</td>
<td></td>
</tr>
<tr>
<td>Smith (71) 2008 South Africa Cohort</td>
<td>39 HIV-infected</td>
<td>Mean age 60 mo</td>
<td>GMDI</td>
<td>Yes – all started HAART at enrollment. Stavudine, lamivudine and ritonavir or efavirenz</td>
<td>No</td>
<td>Mean cognitive scores were less than the norm at baseline and at 6 mo despite 6 mo of HAART (mean scores 67–78 pre and post-HAART commencement); 33% to 81% subnormal intelligence quotients, 33% abnormal motor function.</td>
<td>Weight-for-height</td>
<td></td>
</tr>
<tr>
<td>Van Rie (72) 2008 Congo Cross-sectional</td>
<td>160 HIV-infected = 35 HIV-exposed-uninfected = 35 HIV-unexposed=90</td>
<td>18–72 mo</td>
<td>BSID, PPVT, SON</td>
<td>Yes, not stated when recruited from HIV treatment and care program so most &lt; 1 mo of HAART at recruitment.</td>
<td>No</td>
<td>Motor and cognitive lower in HIV-infected and HIV-exposed-uninfected children. 60% cognitive delay in HIV-infected versus 40% in HIV-exposed-uninfected. 28.6% motor delay in HIV-infected versus 14.3% HIV-exposed-uninfected. Delay in language expression 84.6%, comprehension 76.7%, P &lt; .01. HIV-infected children aged 18–29 mo performed worse, 91% mental, 82% motor delay, versus 46% and 4% in HIV-infected children aged 30–72 mo. Children presenting before clinically eligible for HAART had better cognitive/motor scores than those presenting with requirement for HAART.</td>
<td>Stunting and wasting higher in the HIV-infected group.</td>
<td></td>
</tr>
<tr>
<td>Leartvanangkui (74) 2008 Thailand Cross-sectional</td>
<td>304 HIV-infected = 25 HIV-exposed-uninfected = 279</td>
<td>0–5 y</td>
<td>DDST</td>
<td>Yes, not stated when but part of PMTCT program</td>
<td>No</td>
<td>Gross motor and language delay in HIV-infected children, fine motor and language delay in HIV-exposed-uninfected.</td>
<td>Stunting and wasting prevalent in the HIV-infected group.</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Location</td>
<td>Study Type</td>
<td>n</td>
<td>Groups Studied</td>
<td>Age at Entry</td>
<td>Development Scale</td>
<td>Exposure to ARVs</td>
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<tr>
<td>Ferguson (67)</td>
<td>2009</td>
<td>South Africa 2008</td>
<td>Cross-sectional</td>
<td>86</td>
<td>HIV-infected = 51 HIV-exposed-uninfected = 35</td>
<td>1–33 mo</td>
<td>BSID</td>
<td>39.2% antenatally.</td>
</tr>
<tr>
<td>Laughton (69)</td>
<td>2009</td>
<td>South Africa 2009</td>
<td>Cross-sectional</td>
<td>115</td>
<td>HIV-infected = 92 HIV-exposed-uninfected = 28 HIV-unexposed = 34</td>
<td>10–15 mo</td>
<td>GMDI</td>
<td>Yes, not stated when</td>
</tr>
<tr>
<td>Potterton (70)</td>
<td>2009</td>
<td>South Africa 2001</td>
<td>Cohort</td>
<td>122</td>
<td>All HIV-infected</td>
<td>&lt;2.5 y, mean age 18.5 mo</td>
<td>BSID</td>
<td>Not stated if antenatally. 18 children receiving HAART</td>
</tr>
<tr>
<td>Kandawasvika (68)</td>
<td>2011</td>
<td>Zimbabwe 2010</td>
<td>Cohort</td>
<td>593</td>
<td>HIV-infected = 16 HIV-exposed-uninfected = 577</td>
<td>&lt;12 mo</td>
<td>BINS</td>
<td>Yes- single dose nevirapine in labor, not stated if postnatally</td>
</tr>
</tbody>
</table>

BINS, Bayley Infant Developmental Screener; BSID, Bayley Scales of Infant Development; DDST, Denver Developmental Screening Tool; GMDI, Griffiths Mental Developmental Index; MDI, Mental Developmental Index; PDI, Psychomotor Developmental Index; PI, protease inhibitor; PPVT, Peabody Picture Vocabulary Test; SON, Snijers-Oomen Nonverbal.
demonstrated a greater proportion of floor scores (scores 3 SD below the population mean or less; ie, scores of <49).

Studies that investigated the effects of other variables known to affect neurodevelopment independent of HIV status reported that prematurity, low birth weight, low weight-for-height scores, and low maternal education were all associated with poorer mean neurodevelopmental scores in HIV-infected infants by the age of 12 months compared with the population mean. In general, even when adjusting for these variables, HIV-infected infants demonstrated mean scores >1 SD below the population mean by the age of 12 months. Those infants with worse disease stage and higher viral loads appeared to be at greatest risk of neurodevelopmental impairment.45,51,64

The prevalence of HIV-infected infants’ exposure to ARVs in utero ranged from 39.2% to 96.6%.50,55 In HIV-infected and HIV-exposed-uninfected infants exposed to ARVs in utero, mean mental scores ranged from 85 to 96 and mean motor scores from 75.0 to 96.5.50,55 Lindsey et al55 noted that infants born to mothers treated with ARVs in pregnancy had improved motor scores compared with those born to mothers with no ARVs in pregnancy. They also noted that in the pre-protease inhibitor era, mean mental and motor scores in HIV-infected infants <1 year of age were significantly lower than those among HIV-exposed-uninfected infants and remained lower up to 2 years of age and that these mean scores remained significantly lower than those of HIV-exposed-uninfected infants even after the introduction of a protease inhibitor. Mean scores declined for both HIV-exposed-uninfected infants and HIV-infected infants over time; however, despite this, there was evidence of limited improvement in the HIV-infected infants’ overall mean scores after a protease inhibitor–based treatment had been instigated.55

Despite the widespread use of ARVs in pregnancy, infants with early infection (positive result within 48 hours of life, presumed in utero infection) had lower mean mental and motor scores compared with children diagnosed as infected after 48 hours (presumed peripartum infection).30 and by 24 months, early HIV-infected infants performed significantly less well in both mental and motor mean scores than those infants with later infection.50 There are several limitations to conclusions that can be drawn from this study, namely that it was conducted at a time when maternal HAART in pregnancy was not available and initiation of infants on early treatment was not indicated. Evidence is emerging that infants initiated before the age of 12 weeks have improved locomotor scores compared with those initiated later.62 With the recently changed guidelines recommending early diagnosis and initiation of antiretroviral therapy in infants,42 the impact on the long-term development of these children remains to be documented.

LONG-SURVIVING HIV-INFECTED CHILDREN TREATED WITH ARVS IN RESOURCE-RICH SETTINGS

Early studies of ARV-naive HIV-infected children >30 months of age at study enrollment demonstrated slower disease progression and better clinical outcomes than infants who seemed to have a more rapidly progressive disease and died early.20,76 These studies did not collect data on maternal ARV treatment in pregnancy and describe characteristics of children who had never been treated with ARVs.

In the earliest studies of children aged 3 to 18 years treated with dual therapy, mean global cognitive scores using the Wechsler Intelligence Tests (mean score 100, SD 15)77 and McCarthy Scales of Childhood Abilities (mean score 100, SD 15)78 vary from within the normal range to the neurocognitive impairment range (>2 SDs below the population mean).48,56 A proportion of children with severe disease56,61,62 and high viral loads56,61,62 and those who demonstrated changes, such as cerebral atrophy on computed tomography scan,48,61 displayed mean neurocognitive scores <70, indicating moderate-severe neurocognitive impairment.

Differences between scores before and after treatment instigation are reported by Raskino et al,49 who found that the mean score improved by 11 to 13 points after 24 weeks of treatment with combination zidovudine and didanosine therapy but remained in the range of neurocognitive impairment.

Most early studies of older children treated with any ARV indicated normal global cognitive scores, although all highlighted subtle significant differences in executive function, memory, and verbal skills. It is important to note that there was a large attrition rate because of disease progression, as most of these studies include children treated at a time when children were commenced on ARVs only in advanced disease, with low numbers of children followed for prolonged periods, making generalizability of the results to today’s situation when ARVs are commenced early in infants and at an earlier stage in children problematic.

Recent studies of children treated with a HAART regimen containing a protease inhibitor all indicated normal global cognition mean scores.59,60,65,66 As with earlier studies, subtle significant differences were noted in executive function,59,65 verbal skills,58,59,65 behavior,66 and memory.59,65 This is not universal, however, and a large study by
Smith et al.\textsuperscript{60} reported no significant differences in cognitive scores between groups unless the child had symptomatic disease.

In a small case-control study from the Netherlands (2008), Koekkoek et al.\textsuperscript{65} reported higher, but still below average, global neurocognitive scores among those children with higher CD4 percentage on initiation of HAART and longer duration of HAART compared with children with lower CD4 percentage and shorter duration of treatment.

Language skills were the most widely reported deficit in children older than 3 years. Mean scores from 1 to 2 SD below the population mean were reported in overall language ability,\textsuperscript{56,58} word recognition,\textsuperscript{58} receptive vocabulary,\textsuperscript{61} expressive language,\textsuperscript{58} and verbal fluency.\textsuperscript{65} Although language skills continued to develop, this appeared to be at a slower rate than in HIV-exposed-uninfected children, even taking into account the effect of home circumstances and caregiver arrangements and irrespective of treatment.\textsuperscript{58}

Jeremy et al.\textsuperscript{69} reported no improvement in overall neurocognitive score after commencement with protease inhibitor-based HAART, but noted improvement in verbal scores compared with pretreatment assessment. It is of note that a large proportion of children were tested in a language other than their mother tongue (range 9% to 75%).\textsuperscript{58,59,65} The effects of being assessed in a second language or via an interpreter on language scores have been reported in only 1 study.\textsuperscript{60}

\textbf{HIV-EXPOSED-UNINFECTED CHILDREN IN RESOURCE-RICH SETTINGs}

Few studies have evaluated the effects of perinatal exposure to HIV and ARVs on the neurodevelopment of children who are HIV-exposed-uninfected. Interpretation of these results was difficult because of the heterogeneity of the study populations in terms of sample size (range 44–1694 subjects), sociodemographics, and percentage of maternal substance misuse, together with a lack of clarity surrounding length of maternal antiretroviral therapy in pregnancy. Most studies do not consider results compared with a matched control group, but rather use normative data from the standardization of the neurodevelopmental instrument as a comparison. The scales used are not normed to socioeconomically disadvantaged groups; hence, it is difficult to interpret whether the results reported are a result of social disadvantage, HIV exposure, or ARV exposure.

Studies in early infancy and up to the age of 2 years have not demonstrated any global developmental delay in HIV-exposed-uninfected children once variables such as maternal substance misuse were allowed for.\textsuperscript{44,46–48,50,53–55,60,61} However, it appears that subtle deficits in cognition, motor function, expressive and receptive language, and behavior may be present in older children manifesting during the preschool years (ages 3–5 years).\textsuperscript{58}

\textbf{DEVELOPMENTAL OUTCOMES IN HIV-INFECTED CHILDREN IN RESOURCE-POOR SETTINGs}

The association between HIV infection and neurodevelopmental impairment in infants and children in resource-poor settings is not well described. In contrast to resource-rich settings, where prevention of mother-to-child transmission programs are widespread and infants are predominantly formula fed, children in resource-poor settings are, until very recently, less likely to have been exposed to ARVs in utero and early life and are still predominantly breastfed. In ARV-naive children, neurodevelopmental deficits were reported in 6% to 40% of HIV-infected children in resource-poor settings, depending on disease stage.\textsuperscript{79,80} A direct comparison of studies of children exposed to HIV/ARVs in utero and early life was limited by the use of different methodological designs and the variety of developmental screening and diagnostic tools used: Denver Developmental Scale Test (percentage fail scores)\textsuperscript{81}; Cognitive Adaptive Test, Clinical Linguistics and Auditory Milestones (percentage fail scores)\textsuperscript{62}; Bayley Scales of Infant Development; McCarthy Scales of Childhood Abilities; and Griffiths Mental Development Scale\textsuperscript{63} (all mean 100 SD 15). In addition, comparisons were hampered by adaptations of these tools, including nonvalidated translation into local language and substitution of items with culturally appropriate alternatives.\textsuperscript{67,71} As in resource-rich settings, most studies report results compared with normative data from the standardization of the instrument rather than a matched control group. Further, the effect of ARVs on neurodevelopment is only just emerging, and several studies had only abstracts available, meaning an in-depth analysis of factors that may contribute to neurodevelopmental scores could not be fully assessed.

In comparison with resource-rich settings, a greater proportion of HIV-infected infants in resource-poor settings had scores <2 SD below the mean (16% to 85% in Africa),\textsuperscript{70,72} even when adjusting for birth weight and gestational age.\textsuperscript{72} Infants demonstrating the most severe neurodevelopmental delay were those diagnosed as HIV-infected before the age of 3 months,\textsuperscript{68,72} those with the most advanced disease,\textsuperscript{69,70} those children who were eligible for HAART at the time of presentation,\textsuperscript{67,69,70} and those children with the lowest weight-for-height scores.\textsuperscript{70,71} Only one study reported the effect of prevention of mother-to-child transmission programs on neurodevelopmental outcomes. Kandawasvika et al.\textsuperscript{68}
indicated that maternal treatment with single-dose nevirapine in labor did not influence neurodevelopmental outcomes (adjusted odds ration of high risk of neurodevelopmental impairment with single-dose prophylactic nevirapine 0.9; 95% confidence interval 0.99–1.0). The authors report that background risk of neurodevelopmental impairment was 9.4% in both HIV-infected and HIV-exposed-uninfected infants, probably owing to survival bias in the HIV-exposed-uninfected groups, as the authors speculated that HIV-infected infants with severe disease would not have survived to the 12-month analysis.68

As in resource-rich settings, infants presenting at an earlier disease stage and those commenced on antiretroviral therapy at an earlier age demonstrated some improvement in cognitive and motor developmental scores once commenced on antiretroviral therapy as compared with than those presenting later and with worse clinical disease at instigation of ARVs.72

There are few studies with long-term follow-up of children born to HIV-infected mothers, and such studies have been hampered by high mortality rates in HIV-infected and HIV-exposed-uninfected children.70,72,74 In resource-poor settings where new HIV treatment guidelines recommending early ARV initiation have not been implemented, older children who survive early childhood would tend to have slowly progressing disease. Young children who developed encephalopathy, and those with more advanced disease generally, would be expected to have a shorter life expectancy.84 This selective attrition was seen in some of the earlier studies in resource-poor settings. So the population samples available may be children who were less at risk for central nervous system effects of HIV disease and therefore function at a higher cognitive level. Additionally, these children would have been diagnosed as HIV-infected at a time when early treatment was not yet available, hindering extrapolation to the current situation with early initiation of antiretroviral therapy and improved survival rates.85

Despite subsequent HAART treatment, high levels of motor delay are noted (66.7% to 85%)67,70 and mean motor scores remained >2 SDs below the population mean. In common with resource-rich settings, language delay was also noted in older HIV-infected children with scores remaining below the mean despite 6 months of antiretroviral therapy.71,74 These studies were limited by their small sample sizes.

Few studies in resource-poor settings report results for HIV-exposed-uninfected children. Contrary to studies from United States and Europe, these HIV-exposed-uninfected children in Africa demonstrated cognitive impairment (40%), motor impairment (14.3%), and language expression delay compared with HIV-unexposed infants.72,74 Evidence from Thailand indicated that HIV-exposed-uninfected children assessed using the Denver Developmental Screening Test demonstrated language deficits and fine motor problems compared with their HIV-unexposed peers.74 As with studies of older HIV-infected children in this setting, conclusions were difficult owing to the small sample size and cross-sectional nature of the study.

**CONCLUSIONS**

All studies identified HIV-infected infants as having worse mean neurodevelopmental scores than the reference population in infancy with mean scores consistently more than 1 SD below the population mean, irrespective of whether they had been exposed to ARVs in utero or not. Infants presenting with HIV infection before the age of 3 months had the lowest scores. Since the advent of prevention of mother-to-child-transmission interventions, studies have indicated variable improvement in mean developmental scores in HIV-infected infants exposed to a protease inhibitor–based HAART regimen in utero. Infants commencing treatment before the age of 12 weeks demonstrated better, but still subnormal, mean locomotor scores, than those with delayed treatment. No studies have yet examined the effect of early antiretroviral therapy on cognitive scores.

Older HIV-infected children demonstrated near normal global neurocognitive scores, probably as a result of slower disease progression in this group. However, there is evidence that subtle deficits in higher cognitive functioning (poorer memory, language development) and behavior exist in school-aged children with only limited improvement after initiation of antiretroviral therapy. Evidence suggests that the subtle differences detected in older children in the pre-HAART era may be improved with more effective HAART and that language skills may be improved with a protease inhibitor–based ARV regimen.

The evolution of more effective antiretroviral therapy, from single therapy to HAART, appears to have had a positive impact on mean neurodevelopmental scores in infants and children in the United States and Europe who are HIV-infected and HIV-exposed-uninfected. Lately, results appear to highlight improved outcomes for children treated with ARVs while they are still clinically well. There is also an indication that commencing HAART at an earlier stage of disease benefits long-surviving children. This highlights the importance of the continuing effort to roll out the World Health Organization recommendations42 in resource-poor settings for early and more effective antiretroviral therapy to all eligible pregnant women and their infants.
The extent to which HIV-exposed-uninfected children are affected by in utero exposure to HIV and ARVs remains unclear. This group has only recently become the focus of attention. Although preliminary studies of neurodevelopment from the United States and Europe are reassuring, these studies have yet to be replicated in Africa, where most these children live. Results of the few small studies from sub-Saharan Africa and Asia indicate that in contrast to normal developmental scores seen in populations from the United States, a larger proportion of HIV-exposed-uninfected infants and children displayed global developmental scores 1 to 2 SDs below the population mean, and children appeared to show deficits in language and behavior by the age of 5 years. There are a number of factors that should be considered when reviewing these results. First, access to ARVs in resource-poor settings in pregnancy has only recently become widespread. Although prevention of mother-to-child transmission programs began to be established in sub-Saharan Africa from the early 2000s, UNAIDS estimated that only 9% of eligible HIV-infected pregnant women in resource-poor settings received ARVs in pregnancy in 2004, increasing to ∼33% in 2007. In addition, in low- and middle-income countries, 47% of eligible adults now have access to ARVs. So most children in studies from resource-poor settings included in this review will have been born to mothers who are unwell themselves, with higher viral loads and increased number of associated conditions, such as poor nutrition and concurrent illnesses. This will have had a direct effect on transmission of HIV and ability to care for and stimulate their infants, but also possible longer-term effects including impaired attachment between mother and child, which affects developmental potential, even if the child is HIV-exposed-uninfected. Added factors, such as poverty and early infant malnutrition and growth, also combine to give a more complicated picture of developmental challenges in this environment.

Studies have already indicated the beneficial effects of maternal antiretroviral therapy on child survival and it is probable that in addition to improving child survival, improving maternal health with HAART would benefit developmental outcomes in HIV-exposed-uninfected children. Measures of cognitive, neurologic and behavioral function serve as an indirect means of assessing central nervous system function, along with the more direct measures, such as computed tomography/magnetic resonance imaging. The variety of developmental tools used, lack of matched control groups, and the need for modification and translation into local languages hinders synthesis and summary of data. Robust studies that use validated neurodevelopmental assessment tools are uncommon, and a large number of studies were excluded from our review because such tools were lacking. What is needed is an internationally validated tool that is easy to adapt culturally and can be administered quickly by lay-trained staff in everyday practice to screen and identify developmental delays early.

Interventions to reduce the rate of mother-to-child transmission have been successful in resource-rich settings, and the recent scale up of prevention of mother-to-child transmission programs in resource-poor settings looks set to do the same. Issues remain in unraveling the long-term effect of exposure to HIV and ARVs on HIV-exposed-uninfected children and investigating speech, language, and memory deficits in older children who now have earlier access to therapies that cross the blood-brain barrier. Only a concerted, multidisciplinary approach to diagnosing and treating developmental delay, including antiretroviral therapy, physiotherapy, and early psychological/behavioral therapy will enable these children to reach their full potential.

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