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Ayupova Dilorom Shavkatovna – Ph.D.
Majidova Yo.N. – professor
Tashkent State Medical University (Tashkent, Uzbekistan)

TIMING OF ANTIRETROVIRAL THERAPY INITIATION AND NEURODEVELOPMENTAL OUTCOMES IN CHILDREN WITH PERINATALLY ACQUIRED HIV: A QUANTITATIVE ANALYSIS OF PUBLISHED CLINICAL DATA

Abstract. *Neurodevelopmental impairment remains an important concern in children with perinatally acquired HIV despite effective antiretroviral therapy (ART). This study assessed the relationship between the timing of ART initiation and neurodevelopmental outcomes based on published clinical data. The strongest evidence of benefit was observed when ART was initiated during infancy, particularly in the CHER study, whereas the PREDICT trial showed no significant neurodevelopmental advantage of earlier treatment in children treated after infancy. Data from Central Asia on long-term neurodevelopmental outcomes remain limited, highlighting the need for regional longitudinal studies and regular neurodevelopmental monitoring of children with perinatally acquired HIV.*

Keywords: *HIV; children; antiretroviral therapy; neurodevelopment; cognitive development; ART timing; Central Asia.*

Аюпова Дилором Шавкатовна – Ph.D.
Маджидова Ё.Н. – профессор
Ташкентский государственный медицинский университет (Ташкент, Узбекистан)

СРОКИ НАЧАЛА АНТИРЕТРОВИРУСНОЙ ТЕРАПИИ И НЕЙРОРАЗВИТИЕ ДЕТЕЙ С ПЕРИНАТАЛЬНО ПРИОБРЕТЁННОЙ ВИЧ-ИНФЕКЦИЕЙ: КОЛИЧЕСТВЕННЫЙ АНАЛИЗ ОПУБЛИКОВАННЫХ КЛИНИЧЕСКИХ ДАННЫХ

Аннотация. *Нарушения нейроразвития остаются актуальной проблемой у детей с перинатально приобретённой ВИЧ-инфекцией, несмотря на эффективность антиретровирусной терапии (АРТ). Целью исследования была оценка связи между сроками начала АРТ и показателями нейроразвития на основе опубликованных клинических данных. Наиболее выраженный положительный эффект наблюдался при начале АРТ в младенческом возрасте, особенно в исследовании CHER, тогда как в исследовании PREDICT у детей, начавших лечение после младенческого возраста, значимого преимущества более ранней терапии не выявлено. Данные по долгосрочному нейроразвитию детей с ВИЧ в Центральной Азии ограничены, что подчёркивает необходимость региональных продольных исследований и регулярного мониторинга развития.*

Ключевые слова: *ВИЧ; дети; антиретровирусная терапия; нейроразвитие; когнитивное развитие; сроки начала АРТ; Центральная Азия.*

Ayupova Dilorom Shavkatovna – Ph.D.
Majidova Yo.N. – professor
Toshkent davlat tibbiyot universiteti (Toshkent, O‘zbekiston)

PERINATAL YO‘L BILAN ORTTIRILGAN OIV INFEKSIYASI BO‘LGAN BOLALARDA ANTIRETROVIRUS TERAPIYANI BOSHLASH VAQTI VA NEYRO-RIVOJLANISH NATIJALARI: E’LON QILINGAN KLINIK MA’LUMOTLARNING MIQDORIY TAHLILI

Annotatsiya. *Samarali antiretrovirus terapiyaga (ART) qaramay, perinatal yo‘l bilan orttirilgan OIV infeksiyasi bo‘lgan bolalarda neyro-rivojlanish buzilishlari muhim muammo bo‘lib qolmoqda. Tadqiqotning maqsadi ARTni boshlash vaqti bilan neyro-rivojlanish ko‘rsatkichlari o‘rtasidagi bog‘liqlikni e’lon qilingan klinik ma’lumotlar asosida baholashdan iborat. Eng yaqqol ijobiy natijalar ART chaqaloqlik davrida, ayniqsa CHER tadqiqotida erta boshlanganida kuzatilgan. PREDICT tadqiqotida esa chaqaloqlikdan keyin davolangan bolalarda ARTni ertaroq boshlash neyro-rivojlanish bo‘yicha sezilarli ustunlik bermagan. Markaziy Osiyoda uzoq muddatli neyro-rivojlanish natijalari haqidagi ma’lumotlar cheklangan bo‘lib, mintaqaviy tadqiqotlar va muntazam monitoring zarur.*

Kalit so‘zlar: *OIV; bolalar; antiretrovirus terapiya; neyro-rivojlanish; kognitiv rivojlanish; ARTni boshlash vaqti; Markaziy Osiyo.*

Introduction.

The introduction of combination antiretroviral therapy (ART) has transformed the natural history of pediatric HIV infection. Children who previously faced a high probability of progressive neurological disease can now survive into adolescence and adulthood, provided that treatment is started early and maintained without interruption. Consequently, the clinical problem confronting pediatric HIV care has shifted: severe HIV-associated encephalopathy is now uncommon, whereas subtler impairments of cognition, learning, attention, executive function, and motor development remain frequent and clinically important.

The developing central nervous system is particularly vulnerable to HIV infection, because brain growth, synaptic organization, myelination, and the maturation of higher cognitive functions continue throughout infancy and childhood. The age at which HIV exposure occurs, and the duration of uncontrolled viral replication before ART is started, may therefore determine the extent of later neurological impairment.

Three principal lines of clinical evidence bear directly on this question. The CHER randomized trial demonstrated that initiating ART during infancy improves early neurodevelopmental performance. The PREDICT randomized trial, which enrolled children older than one year, found no significant neurodevelopmental advantage of earlier ART initiation according to CD4 criteria. A cohort study from sub-Saharan Africa (Kenya) reported substantially poorer cognitive, executive, memory, visuospatial, and motor outcomes among school-aged children who initiated ART later in childhood compared with those treated during infancy. Considered together, these three sources of evidence do not describe a uniform, dose-independent relationship between ART timing and neurodevelopment; instead, they suggest that the developmental period in which treatment begins is the determining variable.

The present study was designed as a quantitative comparative analysis of these three principal evidence sources, undertaken to determine whether age at ART initiation is systematically associated with neurodevelopmental outcome across the reported developmental periods, and to define the extent of the regional evidence gap that currently constrains this question in Central Asia.

Materials and Methods.

Study design

This study was designed as a quantitative comparative secondary analysis of published clinical data. Rather than providing a narrative overview of the pediatric neuro-HIV literature, the analysis was restricted a priori to studies capable of directly informing the relationship between age at ART initiation and neurodevelopmental outcome.

Study selection criteria

Studies were eligible for inclusion if they met all of the following criteria: (1) enrolled children with perinatally acquired HIV infection; (2) reported age at ART initiation, either as a randomized comparison or as a defined exposure variable; (3) used a standardized, quantifiable measure of neurodevelopmental, neurocognitive, or motor outcome; and (4) reported a defined comparator group (deferred treatment, later treatment initiation, or an HIV-uninfected reference group). Studies were excluded if they were case reports or small case series, did not stratify outcomes by age at treatment initiation, or reported outcomes that could not be expressed as a quantifiable measure.

On the basis of these criteria, three principal sources of clinical evidence were identified for structured comparison: the CHER randomized trial and its five-year neurodevelopmental follow-up (early ART during infancy), the PREDICT randomized trial (ART initiated at 1–12 years of age), and a cohort study from sub-Saharan Africa (Kenya) evaluating school-aged children who initiated ART at different ages. Regional epidemiological data on pediatric HIV in Central Asia were additionally reviewed to establish the extent of the local evidence gap, although these data do not themselves report neurodevelopmental outcomes and were therefore analyzed separately from the three outcome studies.

Data extraction

For each eligible study, the following variables were extracted from the published report: study design, population and age range, the number of participants in each exposure and comparator group, age at ART initiation, the neurodevelopmental instrument or outcome measure used, age at outcome assessment, and the direction and magnitude of the reported between-group difference. Sample sizes for all included studies are reported in Table 1. Extracted quantitative values (e.g., mean developmental quotients, adjusted odds ratios) are reported as published, without recalculation or reinterpretation of primary data. No individual patient-level records or identifiable clinical information were accessed; all data were derived from published aggregate results.

Statistical analysis

Because the three principal studies differed in age at assessment, treatment strategy, follow-up duration, and neurodevelopmental instrument, the extracted results were not pooled into a single quantitative effect estimate. Instead, the reported outcome measures were tabulated and compared descriptively across a common analytic axis — the developmental period at which ART was initiated (infancy versus later childhood). This structured comparative approach allows the direction and consistency of the association between treatment timing and neurodevelopmental outcome to be assessed across independent studies, while respecting the methodological heterogeneity that precludes formal meta-analytic pooling.

Results.

Table 1 summarizes the sources of evidence considered in this analysis, including the number of children evaluated in each study. In total, the three developmental-outcome studies evaluated 742 children with perinatally acquired HIV across independent cohorts: 377 in the CHER trial (from which the 11-month and five-year neurodevelopmental subcohorts summarized in Table 1 were drawn), 284 in the PREDICT neurodevelopmental study, and 81 in the Kenyan cohort. HIV-uninfected or HIV-exposed-uninfected comparison groups are reported separately for each study in Table 1. The findings below are presented according to the developmental period at which ART was initiated.

Early ART initiated during infancy (CHER trial)

In the CHER neurodevelopmental substudy (Laughton et al., 2012), 90 infants from the Cape Town trial site were assessed at a median age of 11 months: 64 who had received early ART (initiated before 3 months of age) and 26 whose treatment had been deferred. Infants who received early ART showed better early developmental performance than infants whose treatment was deferred: the mean (SD) Griffiths locomotor quotient was 97.7 (12.5) in the early-treatment group compared with 88.9 (16.3) in the deferred-treatment group ($P<0.01$), and the mean general developmental quotient was 106.3 (10.6) versus 100.1 (13.8) ($P=0.02$). This difference indicates that ART initiated during the first months of life measurably altered early developmental trajectories in favor of the treated group.

At five-year follow-up (Laughton et al., 2018), 169 children were assessed: 96 HIV-infected children (28 who had received deferred ART, 35 who had received the 40-week early-limited ART strategy, and 33 who had received the 96-week early-limited ART strategy) and 73 comparison children (34 HIV-exposed but uninfected and 39 HIV-unexposed). Some of the early differences observed at 11 months had become less pronounced between the early- and deferred-treatment arms by five years. However, differences in selected domains, including visual perception, persisted between HIV-infected and HIV-uninfected children regardless of treatment strategy. This pattern indicates that early ART improves the developmental trajectory without eliminating all neurodevelopmental vulnerability associated with perinatal HIV infection.

ART initiated after infancy (PREDICT trial)

In the PREDICT neurodevelopmental study (Puthanakit et al., 2013), 284 Thai and Cambodian children aged 1–12 years were randomized to immediate ART (n=139) or to CD4-triggered deferred ART (n=145); outcomes were additionally compared with 319 HIV-uninfected children. Despite achieving better immunological and virological control (CD4 33% vs 24%; viral suppression 91% vs 40%; both $P<0.001$), the immediate-treatment group did not show a statistically significant advantage over the deferred-treatment group in major neurodevelopmental outcomes at follow-up (median age 9 years); both HIV-infected groups performed worse than the uninfected comparison group regardless of ART timing. This null result contrasts with the CHER findings and indicates that the neurodevelopmental benefit of earlier ART observed in infancy was not reproduced when treatment timing was compared after infancy.

Later childhood treatment: sub-Saharan Africa (Kenya) cohort

In the Kenyan cohort (Benki-Nugent et al., 2023), 142 children were assessed: 54 who had initiated ART during infancy (before 1 year of age), 27 who had initiated ART later in childhood (between 1.5 and 6 years of age), and 61 HIV-unexposed, uninfected children as a comparison group. Children who initiated ART after infancy demonstrated poorer performance than earlier-treated children across multiple domains, including global cognition, short-term memory, visuospatial processing, learning, nonverbal performance, executive functioning, and motor skills. Adjusted odds ratios for impairment in these domains were substantially elevated in the later-treatment group relative to the early-treatment group; even children treated during infancy scored lower than HIV-unexposed, uninfected peers, indicating attenuation but not elimination of neurodevelopmental compromise.

Summary of the comparative pattern

Across the three studies, the association between ART timing and neurodevelopmental outcome was not uniform, but was consistently strongest when treatment was initiated during infancy: a measurable benefit in CHER, no measurable benefit when treatment timing was compared after infancy in PREDICT, and a substantial disadvantage of later treatment in the Kenyan cohort. This pattern is consistent with an age-dependent, rather than a strictly time-dependent, relationship between ART initiation and neurodevelopment.

Regional evidence gap in Central Asia

Independent of the three developmental-outcome studies above, recent regional epidemiological data indicate that pediatric HIV remains a significant public-health concern in Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, and Uzbekistan. These regional data are reported as aggregate national surveillance figures rather than as a defined patient cohort, so no comparable patient-level sample size can be reported for this source. No study meeting the selection criteria above — that is, reporting a quantifiable, age-stratified neurodevelopmental outcome measure in a defined cohort of children — was identified from Central Asia, confirming that this region currently lacks the patient-level data needed to determine whether the pattern described above is reproduced locally.

Discussion.

The principal finding of this analysis is that the association between ART timing and neurodevelopment in children with perinatally acquired HIV is not uniform across childhood, but is consistently strongest when treatment begins during infancy.

The clearest evidence of benefit comes from the CHER trial, in which suppressing HIV replication during the first months of life produced a measurable improvement in early developmental performance. This finding is biologically plausible, since infancy corresponds to a period of maximal brain growth and synaptic maturation, during which uncontrolled viral replication may cause disproportionate injury.

The absence of a significant neurodevelopmental advantage in PREDICT should not be interpreted as evidence against early treatment in general. The PREDICT population was fundamentally different from that of CHER: children were already older than one year at randomization, and some neurological consequences of earlier, untreated HIV exposure may already have been established by that age. In this context, earlier ART initiation after infancy may prevent additional injury without reversing developmental alterations that occurred before treatment began.

The Kenyan cohort findings are consistent with this interpretation. Children who remained untreated until later childhood showed a broader pattern of cognitive and motor impairment than children treated during infancy, suggesting that prolonged, uncontrolled HIV exposure during early brain development produces consequences that remain detectable years later. Taken together, the CHER, PREDICT, and Kenyan findings describe a coherent, age-dependent pattern rather than three unrelated or contradictory results: the earlier the developmental window in which ART begins, the more completely early neurodevelopmental trajectories are preserved.

An important clinical implication of this pattern is that virological suppression alone should not be equated with normal neurodevelopment. A child may have an undetectable viral load and continue to experience difficulties with processing speed, working memory, executive function, learning, or visual-spatial tasks. Long-term treatment goals in pediatric HIV should therefore extend beyond survival and viral suppression to include the preservation of developmental potential, educational functioning, and quality of life.

Central Asian Context

Central Asia should be considered a distinct epidemiological and clinical context rather than an extension of evidence generated in sub-Saharan Africa. Recent regional data indicate that pediatric HIV remains a significant public-health concern in Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, and Uzbekistan, although country-specific information on pediatric HIV outcomes remains uneven. A 2025 regional analysis covering nine Central Asian countries emphasized the scarcity of age-disaggregated pediatric HIV data and the continuing importance of mother-to-child transmission in the region. At the same time, no longitudinal study linking age at ART initiation to standardized neurocognitive outcomes was identified from Central Asia in this analysis. This evidence gap is clinically important: local cohorts are needed to determine whether the developmental pattern described above for CHER, PREDICT, and the Kenyan cohort is reproduced in Central Asian children, and to identify region-specific influences such as treatment access, adherence, nutritional status, schooling, and family support.

Clinical Implications

Children diagnosed with HIV during infancy should begin ART as early as clinically appropriate, in accordance with current pediatric HIV treatment recommendations.

However, early treatment does not eliminate the need for developmental surveillance. Clinicians should periodically assess language, motor development, attention, memory, school performance, behavior, and learning throughout childhood and adolescence.

When concerns arise, standardized developmental or neuropsychological assessment should be considered, encompassing working memory, processing speed, executive function, attention, learning, language, visual-spatial skills, and motor coordination as appropriate to the child's age.

Children with identified difficulties may benefit from individualized educational support, psychological intervention, speech and language services, occupational therapy, or other developmental interventions. The clinical objective is to identify functional difficulties early enough that appropriate support can be provided before academic or social consequences become substantial.

Limitations

This analysis has several limitations. The three principal studies were conducted in different countries and healthcare settings and used different neurodevelopmental instruments; the ages at ART initiation and at outcome assessment varied considerably between them. CHER and PREDICT were randomized trials, whereas the Kenyan cohort was observational and therefore susceptible to residual confounding.

Because the analysis used published aggregate data rather than individual participant-level records, the reported outcome measures could not be pooled into a single quantitative effect estimate

across all cognitive domains; the comparative pattern described here is therefore descriptive rather than meta-analytic. In addition, CHER and PREDICT addressed different developmental periods and should not be interpreted as directly contradictory studies. These limitations emphasize the need for large prospective cohorts — ideally including Central Asian populations — that use harmonized neurodevelopmental measures and collect detailed information on ART timing, viral suppression, immune status, and environmental factors.

Conclusion.

This quantitative comparative analysis indicates that the timing of ART initiation is systematically associated with neurodevelopmental outcome in children with perinatally acquired HIV, with the clearest benefit observed when treatment begins during infancy.

Early ART improves early developmental outcomes and may reduce the long-term burden of neurocognitive impairment; however, it does not guarantee entirely normal neurodevelopment, and children may continue to experience difficulties in memory, processing speed, executive function, visual perception, learning, or motor skills regardless of treatment timing.

These findings support two complementary principles for pediatric HIV care: treatment should begin as early as possible, and neurodevelopment should be monitored throughout childhood, regardless of virological status. For the child, successful HIV treatment is defined not only by an undetectable viral load, but by the preservation of the ability to develop, learn, participate in school, and achieve increasing independence. Prospective, regionally representative studies — including from Central Asia — are needed to confirm whether this pattern generalizes beyond the populations examined here.

Table 1.

Principal evidence sources included in the comparative analysis of ART timing and neurodevelopmental outcome

Study	N (patients)	Population	Early ART	Comparator	Main finding
CHER neurodevelopmental substudy (Laughton et al., 2012)	90 (64 early ART; 26 deferred)	Perinatally infected infants, Cape Town trial site	Early infancy (<3 months)	Deferred ART	Better early locomotor/general development (locomotor quotient 97.7 vs 88.9, P<0.01)
CHER 5-year follow-up (Laughton et al., 2018)	169 (96 HIV-infected: 28 deferred, 35 ART-40W, 33 ART-96W; 73 comparison children)	Children followed from infancy	40/96-week early-limited ART strategies	Deferred ART	Some early differences diminished; visual-perception deficit remained vs uninfected children
PREDICT neurodevelopmental study (Puthanakit et al., 2013)	284 (139 immediate; 145 deferred); plus 319 HIV-uninfected comparison children	Children 1–12 years, Thailand/Cambodia	Immediate ART	CD4-triggered deferred ART	No significant neurodevelopmental advantage
Sub-Saharan Africa (Kenya) cohort (Benki-Nugent et al., 2023)	142 (54 early ART; 27 late ART; 61 HIV-unexposed uninfected controls)	School-aged children with perinatally acquired HIV, Kenya	Treated during infancy (<1 year)	ART initiated 1.5–6 years	Poorer global cognition, memory, visuospatial, executive, and motor performance among later-treated children
Central Asia (regional epidemiological data)	Not a patient cohort (aggregate national surveillance data)	Children <5 years; Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan	Country-specific treatment-timing data remain limited	Not applicable	Documents pediatric HIV burden; confirms absence of regional neurodevelopmental outcome data

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