Nevirapine (NVP, Viramune)

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Formulations

Oral Suspension: 10 mg/mL

Tablets: Immediate-release 200-mg tablets; extended-release (XR) 100-mg and 400-mg tablets

Generic Formulations

- 10-mg/mL suspension
- Immediate-release 200-mg tablets
- XR 400-mg tablets

The oral suspension formulation of nevirapine (brand name Viramune) is not typically stocked in local pharmacies or hospitals. Clinicians should direct pharmacies to ask their drug wholesaler to order it from the Boehringer-Ingleheim distribution center. The distribution center should be able to ship the formulation directly to the pharmacy.

Dosing Recommendations

Note: Nevirapine (NVP) is often used as part of newborn antiretroviral regimens to prevent perinatal transmission of HIV. See Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection.

Child and Adolescent Dose

- In most situations, NVP is given once daily for 2 weeks to allow autoinduction of the enzymes involved in its metabolism. This may not be necessary in children aged <2 years.[a]
- See Special Considerations for Dosing: Neonates and Premature Infants below.

Immediate-Release Tablets and Oral Suspension

Gestational Age of 32 to <34 Weeks

- Birth to age 2 weeks: NVP 2 mg/kg per dose twice daily (no lead-in dosing)[a]
- Age 2 to 4 weeks: NVP 4 mg/kg per dose twice daily
- Age 4 to 6 weeks: NVP 6 mg/kg per dose twice daily
- Age >6 weeks: NVP 200 mg/m^2 of body surface area (BSA) per dose twice daily; only make this dose increase for infants with confirmed HIV infection.
- This dosing strategy is recommended by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) based on the review of pharmacokinetic (PK) modeling and simulation data. This dosing strategy has not been evaluated in clinical trials and is not approved by the U.S. Food and Drug Administration (FDA).

Selected Adverse Events

- Rash, including Stevens-Johnson syndrome
- Symptomatic hepatitis, including fatal hepatic necrosis[b]
- Severe systemic hypersensitivity syndrome with potential for multisystem organ involvement and shock

Special Instructions

- The oral suspension must be shaken well before administering, and it should be stored at room temperature.
- NVP can be given with or without food.
- NVP-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14-day lead-in period, do not increase the dose until the rash resolves (see Major Toxicities below).
- Extended-release tablets must be swallowed whole. They cannot be crushed, chewed, or divided.
- If NVP dosing is interrupted for >14 days, NVP should be restarted with once-daily dosing for 14 days, followed by escalation to the full twice-daily regimen (see Dosing Considerations: Lead-In Dosing below).

Gestational Age of 34 to <37 Weeks

- Birth to age 1 week: NVP 4 mg/kg per dose twice daily (no lead-in dosing)[a]
- Age 1 week to 4 weeks: NVP 6 mg/kg per dose twice daily
- Age >4 weeks: NVP 200 mg/m^2 of BSA per dose twice daily; only make this dose increase for infants with confirmed HIV infection.
- This dosing strategy is recommended by the Panel based on the review of PK and safety data on this regimen from clinical trials. This dosing strategy is not approved by the FDA.

Gestational Age of ≥37 Weeks to Age of <1 Month

- Birth to age 4 weeks: NVP 6 mg/kg per dose twice daily (no lead-in dosing)[a]
- Age >4 weeks: NVP 200 mg/m^2 of BSA per dose twice daily; only make this dose increase for infants with confirmed HIV infection.
- This dosing strategy is recommended by the Panel based on the review of PK and safety data on this regimen from clinical trials. This dosing strategy is not approved by the FDA.

Aged ≥1 Month to <8 Years

- NVP 200 mg/m^2 of BSA per dose twice daily after lead-in dosing.[a] In children aged ≤2 years, some experts initiate NVP without lead-in dosing (maximum dose of immediate-release tablets is NVP 200 mg twice daily).

Aged ≥8 Years

- NVP 120 mg to 150 mg/m^2 of BSA per dose twice daily after lead-in dosing[a] (maximum dose of immediate-release tablets is NVP 200 mg twice daily).
- When adjusting the dose for a growing child, the absolute dose need not be decreased as the child reaches age 8 years; rather, the absolute dose can be left static to achieve the appropriate mg-per-m^2 dose as the child grows, assuming no adverse effects emerge.

Extended-Release Tablets

Aged ≥6 Years

- Patients aged ≥6 years who are already taking immediate-release NVP tablets twice daily can be switched to extended-release NVP tablets without lead-in dosing.[a]

Body Surface Area Dosing for Extended-Release NVP Tablets

Body Surface Area	Once-Daily Dose
0.58 m^2 to 0.83 m^2	NVP 200 mg (two 100-mg tablets)
0.84 m^2 to 1.16 m^2	NVP 300 mg (three 100-mg tablets)
≥1.17 m^2	NVP 400 mg (one 400-mg tablet)

- Most cases of NVP-associated hepatic toxicity occur during the first 12 weeks of therapy; frequent clinical and laboratory monitoring, including liver function tests, is important during this period (see Major Toxicities below).

Metabolism/Elimination

- NVP is a substrate and inducer of cytochrome P450 (CYP) 3A4 and CYP2B6. More than 80% of a NVP dose is eliminated in urine as uridine diphosphate glucuronosyltransferase (UGT)–derived glucuronidated metabolites.

NVP Dosing in Patients with Hepatic Impairment

- NVP should not be administered to patients with moderate or severe hepatic impairment.

NVP Dosing in Patients with Renal Failure Who Are Receiving Hemodialysis

- An additional dose of NVP should be given following each dialysis session.

Adolescent and Adult Dose • NVP 200 mg twice daily or NVP 400 mg with the extended-release tablets once daily after lead-in dosing.[a,b] NVP Used in Combination with Lopinavir/Ritonavir (LPV/r) • A higher dose of LPV/r may be needed in patients who also are receiving NVP (see the Lopinavir/Ritonavir section).	

[a] NVP is usually initiated at a lower dose that is increased in a stepwise fashion. NVP induces cytochrome P450 metabolizing enzymes, which results in increased drug clearance. The stepwise increase in dose decreases the occurrence of rash. Clinicians generally should initiate therapy with the immediate-release tablet formulation once daily instead of twice daily for the first 14 days of therapy. If no rashes or other adverse effects emerge after 14 days of therapy, increase the dose of NVP to the age-appropriate full dose of the immediate-release tablet formulation administered twice daily. For example, the recommended oral dose for pediatric patients aged ≥1 month to <8 years is NVP 200 mg/m^2 of BSA once daily for the first 14 days, followed by NVP 200 mg/m^2 of BSA twice daily thereafter. However, in children aged ≤2 years, some experts initiate NVP without lead-in dosing (see the Dosing Considerations: Lead-In Dosing and Special Considerations for Dosing: Neonates and Premature Infants sections below). In patients who are already receiving the full twice-daily dose of the immediate-release tablets, extended-release tablets can be used without the lead-in period. Patients must swallow extended-release tablets whole. They must not be chewed, crushed, or divided. Patients must never take more than one form of NVP at the same time. The dose should not exceed NVP 400 mg daily.

[b] Severe life-threatening and, in rare cases, fatal hepatotoxicity—including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure—has occurred in patients who were taking NVP. These toxicities are less common in children than adults. Most cases occur during the first 12 weeks of therapy and may be associated with rash or other signs or symptoms of hypersensitivity reaction (HSR). NVP should be discontinued and not restarted in children or adults who develop symptomatic hepatitis, severe transaminase elevations, or HSRs.

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- *Metabolism:* Nevirapine (NVP) is metabolized by and induces hepatic CYP3A and CYP2B6; autoinduction of metabolism occurs in 2 to 4 weeks of NVP dosing, leading to a 1.5-fold to twofold increase in NVP clearance. Multiple drug interactions with NVP are possible. Some genetic polymorphisms of CYP2B6 are associated with increased NVP plasma concentrations. The prevalence of CYP2B6 polymorphisms varies among populations and may contribute to differences in NVP exposure. See the Efavirenz section for more information on how polymorphisms can alter metabolic enzyme activity.
- NVP should not be coadministered to patients who are receiving atazanavir (ATV) (with or without ritonavir) because NVP substantially decreases ATV exposure.
- NVP increases the metabolism of lopinavir (LPV). A dose adjustment of LPV is recommended when the two drugs are coadministered (see the Lopinavir/Ritonavir section).
- Before NVP is initiated, a patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities

The following toxicities are seen with chronic dosing, not during single-dose NVP prophylaxis.

- *More common:* Skin rash (some severe cases have required hospitalization, and some cases have been life-threatening, including instances of Stevens-Johnson syndrome and toxic epidermal necrolysis), fever, nausea, headache, and elevated hepatic transaminases. In the two largest case series of NVP-induced Stevens-Johnson syndrome in children, the incidence rate was estimated between 1.4% and 7.1%.[1,2] NVP should be **discontinued and not restarted** in children or adults who develop severe rash, rash with constitutional symptoms (i.e., fever, oral lesions, conjunctivitis, or blistering), or rash with elevated levels of hepatic transaminases. NVP-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14-day lead-in period, do not increase the dose until rash resolves. However, the risk of developing NVP resistance with extended lead-in dosing is unknown, and this concern must be weighed against the current antiviral response and a patient's overall ability to tolerate the regimen.
- *Less common (more severe):* These toxicities are less common in children than adults. Most cases occur during the first 12 weeks of therapy and may be associated with rash or other signs or symptoms of hypersensitivity reaction (HSR). Risk factors for NVP-related hepatic toxicity in adults include baseline elevation in serum transaminase levels, hepatitis B or hepatitis C virus infection, female sex, and higher CD4 T lymphocyte (CD4) cell count at time of therapy initiation (CD4 count >250 cells/mm^3 in adult females and >400 cells/mm^3 in adult males). Children with CD4 percentages >15% have a threefold increase in the risk of rash and hepatotoxicity after initiating NVP.[3] HSRs have been reported, including, but not limited to, severe rash or rash accompanied by fever, blisters, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, and significant hepatic abnormalities. NVP **should be discontinued and not restarted** in children or adults who develop symptomatic hepatitis, severe transaminase elevations, or HSRs.
- *Less common (more severe):* In a cross-sectional study of 201 children with HIV aged 6 to 16 years, 43% of whom had hypertension, the use of NVP was associated with left ventricular hypertrophy (LVH) (adjusted odds ratio 3.14; confidence interval 1.13–8.72; $P = 0.03$) but not left ventricular diastolic dysfunction.[4] The median duration on antiretroviral therapy (ART) in this cohort was 4.7 years (interquartile range 2.6–6.4 years). Most participants (76.6%) were receiving a regimen that included two nucleoside reverse transcriptase inhibitors and a non-nucleoside reverse transcriptase inhibitor (NNRTI). However, the use of NVP was not associated with LVH in a more recent study by the same authors. LVH has been associated with NVP use in adults.[5,6]

Resistance

The International AIDS Society–USA maintains a list of updated resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

NVP is approved by the U.S. Food and Drug Administration (FDA) for treatment of HIV in children from infancy (aged ≥15 days) onward and remains a mainstay of ART, especially in resource-limited settings.[7-15] The extended-release tablet formulation has been approved by the FDA for use in children aged ≥6 years.

Efficacy in Clinical Trials

Randomized clinical trials in children have demonstrated that lopinavir/ritonavir (LPV/r) is superior to NVP in young children but not in older children. IMPAACT P1060 demonstrated the superiority of LPV/r over NVP in children aged <3 years, as have observational studies. PENPACT-1 and PROMOTE-pediatrics showed no differences in virologic outcomes between an NNRTI-based regimen (with either NVP or efavirenz [EFV]) and a protease inhibitor (PI)–based regimen in older children with HIV.[16-22]

In infants and children who were previously exposed to a single dose of NVP to prevent perinatal HIV transmission, NVP-based ART is less likely to control viral load than LPV/r-based ART. In IMPAACT P1060, 153 children with HIV and previous exposure to NVP for perinatal prophylaxis (mean age 0.7 years) were randomly assigned to treatment with zidovudine (ZDV) and lamivudine (3TC) plus either NVP or LPV/r. At 24 weeks post-randomization, 24% of children in the NVP arm had experienced virologic failure compared with 7% of children in the LPV/r arm ($P = 0.0009$); virologic failure was defined as <1 $\log_{10}$ decrease in HIV RNA during Weeks 12 to 24 or HIV RNA >400 copies/mL at Week 24. When all primary endpoints were considered, including virologic failure, death, and treatment discontinuation, the PI arm remained superior; 40% of children in the NVP arm met a primary endpoint, compared with 22% of children in the LPV/r arm ($P = 0.027$).[19] Similar results were reported in a randomized trial that compared NVP and LPV/r in children aged 6 to 36 months who had not been previously exposed to NVP. This finding suggests that LPV/r-based therapy is superior to NVP-based therapy for infants, regardless of past NVP exposure.[16]

Extended-release NVP tablets (400 mg) were approved by the FDA for use in children aged ≥6 years in November 2012. Trial 1100.1518 was an open-label, multiple-dose, nonrandomized crossover trial performed in 85 pediatric participants with HIV. The participants had received at least 18 weeks of immediate-release NVP tablets and had plasma HIV RNA <50 copies/mL prior to enrollment. Participants were stratified according to age (3 years to <6 years, 6 years to <12 years, and 12 years to <18 years). Participants received immediate-release NVP tablets for 11 weeks. Participants were then treated with NVP extended-release tablets once daily in combination with other antiretroviral (ARV) drugs for 10 days, after which steady-state pharmacokinetics (PK) were determined.[23] Forty participants who completed the initial part of the study were enrolled in an optional extension phase of the trial, which evaluated the safety and antiviral activity of extended-release NVP tablets through a minimum of 24 weeks of treatment. Of the 40 participants who entered the treatment extension phase, 39 completed at least 24 weeks of treatment. After 24 weeks or more of treatment with extended-release tablets,[24] all 39 participants continued to have plasma HIV RNA <50 copies/mL.

General Dosing Considerations

Body surface area (BSA) has traditionally been used to guide NVP dosing in infants and young children. It is important to avoid underdosing NVP, because a single point mutation (K103N) in the HIV genome may confer NNRTI resistance to both NVP and EFV. Younger children (aged ≤8 years) have higher apparent oral clearance than older children. To achieve drug exposures that are comparable to those seen in children aged >8 years, younger children require higher doses of NVP than older children.[12,13] Because of this, it is recommended that children aged <8 years receive NVP 200 mg/m^2 of BSA per dose twice daily (the maximum dose of the immediate-release tablet formulation is NVP 200 mg twice daily) or NVP 400 mg/m^2 of BSA administered once daily as the extended-release tablet formulation (the maximum dose of the extended-release tablet formulation is NVP 400 mg once daily). For children aged ≥8 years, the recommended dose of the immediate-release tablet formulation is NVP 120 mg/m^2 of BSA per dose (with a maximum dose of NVP 200 mg) administered twice daily. The maximum dose of the extended-release tablet formulation is NVP 400 mg once daily for children aged ≥6 years.

When adjusting the dose for a growing child, the milligram dose need not be decreased (from NVP 200 mg to NVP 120 mg/m^2 of BSA) as the child reaches 8 years of age; rather, the milligram dose can be left static if no adverse effects emerge and the dose achieves the appropriate mg/m^2 of BSA dose as the child grows. Some practitioners dose NVP at 150 mg/m^2 of BSA every 12 hours or NVP 300 mg/m^2 of BSA once daily if using the extended-release tablets, regardless of age, as recommended in the FDA-approved product label. Regardless of age, the maximum dose should never exceed NVP 200 mg twice daily for immediate-release formulations of NVP or NVP 400 mg once daily for extended-release formulations of NVP.

Dosing Considerations: Lead-in Dosing

Underdosing during the lead-in period may have potentially contributed to the poorer performance of NVP in the IMPAACT P1060 trial. This potential for underdosing, which can increase the risk of resistance, has led to a re-evaluation of lead-in dosing in children who have never received NVP. Traditionally, NVP is initiated with an age-appropriate dose that is given only once daily instead of twice daily (NVP 200 mg/m^2 of BSA in infants aged ≥15 days and children aged <8 years, using the immediate-release formulations) during the first 2 weeks of treatment to allow the autoinduction of the liver enzymes CYP3A and CYP2B6, which are involved in NVP metabolism.

Studies have previously indicated potential for greater drug toxicity without lead-in dosing; however, most of these studies have been performed in adult cohorts.[25] The CHAPAS-1 trial[26] randomized 211 children to initiate ART with immediate-release NVP without a lead-in dose (participants received an age-appropriate dose twice daily) or with a lead-in dose (participants received an age-appropriate dose once daily) for 2 weeks, followed by the standard twice-daily dosing of the immediate-release formulation of NVP. Children were followed for a median of 92 weeks (with a range of 68–116 weeks), and no difference emerged in the frequency of Grade 3 or 4 adverse events between the two groups. The group that initiated NVP without a lead-in dose had a statistically significant increase in the incidence of Grade 2 rash, but most participants were able to continue NVP therapy after a brief interruption. Through 96 weeks, a similar percentage of participants in both groups reached the CD4 count and virologic failure endpoints.

After children had been on NVP for 2 weeks, investigators conducted a substudy that examined NVP plasma concentrations 3 to 4 hours after a morning dose of NVP. Among children aged <2 years, 3 of

23 children (13%) who initiated at full dose had subtherapeutic NVP levels (<3 mg/L) at 2 weeks compared with 7 of 22 children (32%) who initiated at half dose ($P = 0.16$). No rash events occurred in the substudy group of participants aged <2 years; in the parent CHAPAS study, a strong age effect on rash occurrence was seen, with the risk of rash increasing with age. These findings suggest that a lead-in dose may not be necessary in young patients.[27]

The standard practice has been to reinitiate half-dose NVP for another 2 weeks in children who have interrupted therapy for 7 days or longer; however, given the current understanding of NVP resistance, the half-life of CYP enzymes,[28] and the results of CHAPAS-1, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends restarting full-dose NVP in children who interrupt therapy for 14 days or less.

Special Considerations for Dosing: Neonates and Premature Infants

The PK and safety of NVP during the first weeks of life were evaluated as part of IMPAACT P1115. This study demonstrated that NVP dosed at 6 mg/kg twice daily for infants ≥37 weeks gestational age (GA) and 4 mg/kg twice daily for 1 week and 6 mg/kg twice daily thereafter for infants 34 to <37 weeks GA achieved concentrations appropriate for treatment.[29] Among 438 infants (389 infants ≥37 weeks GA), measured NVP concentrations were above the minimum HIV treatment target (3 mcg/mL) in 90% of infants at Week 1 and 87% of infants at Week 2. Grade 3 and 4 adverse events possibly related to treatment occurred in 7% of infants (with neutropenia and anemia being the most common) but did not lead to NVP cessation.

PK modeling and simulation were performed with partial data from IMPAACT P1106 and P1115 to determine appropriate NVP dosing in premature infants 32 to <34 weeks GA. GA and postnatal age were significantly correlated with NVP oral clearance; thus, the authors recommended a GA-based starting dose for premature infants treated with NVP and a stepwise increase in dosing at 2-week intervals.[30] These data might underestimate potential drug toxicity in infants of 32 to <34 weeks GA because the doses used to develop the model were lower than the doses now recommended. NVP is shown to be safe in infants >34 weeks GA, so the risk of toxicity in infants 32 to <34 weeks GA seems low. The Panel considers that this risk–benefit ratio may justify the use of this dose in premature infants 32 to <34 weeks GA.

The Early Infant Treatment Study in Botswana started 40 infants with HIV ≥35 weeks GA on NVP 6 mg/kg twice daily (without lead-in dosing) along with ZDV and 3TC at a median age 2 days (range 1–5 days). NVP was switched to LPV/r at Week 2, 3, 4, or 5 according to delivery GA. Although NVP trough concentrations were below the therapeutic target (3,000 ng/mL) for 50% of 2-week measurements, 37 of 40 infants (92.5%) had an HIV RNA decline.[31] Among this cohort, 38 of 40 participants survived to 96 weeks with a preserved CD4 count and low reservoir, which was predicted by a low pre-ART reservoir size.[32] Providers who consider initiating treatment in premature infants or in infants aged <2 weeks should weigh the risks and benefits of using unapproved ART dosing and should incorporate case-specific factors, such as exposure to ARV prophylaxis.

References

1. Dziuban EJ, Hughey AB, Stewart DA, et al. Stevens-Johnson syndrome and HIV in children in Swaziland. *Pediatr Infect Dis J*. 2013;32(12):1354-1358. Available at: https://pubmed.ncbi.nlm.nih.gov/23743542.

2. du Toit JD, Kotze K, van der Westhuizen HM, Gaunt TL. Nevirapine-induced Stevens-Johnson syndrome in children living with HIV in South Africa. *South Afr J HIV Med*. 2021;22(1):1182. Available at: https://pubmed.ncbi.nlm.nih.gov/33824730.

3. Kea C, Puthanakit T, et al. Incidence and risk factors for nevirapine-related toxicities among HIV-infected Asian children randomized to starting ART at different CD4%. Abstract MOPE240. Presented at: 6th IAS Conference on HIV Pathogenesis, Treatment, and Prevention; 2011. Rome, Italy,. Available at: https://f1000research.com/posters/1089267.

4. Majonga ED, Rehman AM, Simms V, et al. High prevalence of echocardiographic abnormalities in older HIV-infected children taking antiretroviral therapy. *AIDS*. 2018;32(18):2739-2748. Available at: https://pubmed.ncbi.nlm.nih.gov/30289814.

5. Pombo M, Olalla J, Del Arco A, et al. Left ventricular hypertrophy detected by echocardiography in HIV-infected patients. *Eur J Intern Med*. 2013;24(6):558-561. Available at: https://pubmed.ncbi.nlm.nih.gov/23664642.

6. Majonga ED, Rehman AM, McHugh G, et al. Incidence and progression of echocardiographic abnormalities in older children with human immunodeficiency virus and adolescents taking antiretroviral therapy: a prospective cohort study. *Clin Infect Dis*. 2020;70(7):1372-1378. Available at: https://pubmed.ncbi.nlm.nih.gov/31054255.

7. Janssens B, Raleigh B, Soeung S, et al. Effectiveness of highly active antiretroviral therapy in HIV-positive children: evaluation at 12 months in a routine program in Cambodia. *Pediatrics*. 2007;120(5):e1134-1140. Available at: https://pubmed.ncbi.nlm.nih.gov/17954553.

8. King JR, Nachman S, Yogev R, et al. Efficacy, tolerability, and pharmacokinetics of two nelfinavir-based regimens in human immunodeficiency virus–infected children and adolescents: pediatric AIDS clinical trials group protocol 403. *Pediatr Infect Dis J*. 2005;24(10):880-885. Available at: https://pubmed.ncbi.nlm.nih.gov/16220085.

9. Krogstad P, Lee S, Johnson G, et al. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis*. 2002;34(7):991-1001. Available at: https://pubmed.ncbi.nlm.nih.gov/11880966.

10. Luzuriaga K, McManus M, Mofenson L, et al. A trial of three antiretroviral regimens in HIV-1-infected children. *N Engl J Med*. 2004;350(24):2471-2480. Available at: https://pubmed.ncbi.nlm.nih.gov/15190139.

11. Luzuriaga K, Bryson Y, McSherry G, et al. Pharmacokinetics, safety, and activity of nevirapine in human immunodeficiency virus type 1-infected children. *J Infect Dis*. 1996;174(4):713-721. Available at: https://pubmed.ncbi.nlm.nih.gov/8843207.

12. Luzuriaga K, Bryson Y, Krogstad P, et al. Combination treatment with zidovudine, didanosine, and nevirapine in infants with human immunodeficiency virus type 1–infection. *N Engl J Med*. 1997;336(19):1343-1349. Available at: https://pubmed.ncbi.nlm.nih.gov/9134874.

13. Mirochnick M, Clarke DF, Dorenbaum A. Nevirapine: pharmacokinetic considerations in children and pregnant women. *Clin Pharmacokinet*. 2000;39(4):281-293. Available at: https://pubmed.ncbi.nlm.nih.gov/11069214.

14. Verweel G, Sharland M, Lyall H, et al. Nevirapine use in HIV-1-infected children. *AIDS*. 2003;17(11):1639-1647. Available at: https://pubmed.ncbi.nlm.nih.gov/12853746.

15. Wiznia A, Stanley K, Krogstad P, et al. Combination nucleoside analog reverse transcriptase inhibitor(s) plus nevirapine, nelfinavir, or ritonavir in stable antiretroviral therapy-experienced HIV-infected children: week 24 results of a randomized controlled trial--PACTG 377. Pediatric AIDS Clinical Trials Group 377 Study Team. *AIDS Res Hum Retroviruses*. 2000;16(12):1113-1121. Available at: https://pubmed.ncbi.nlm.nih.gov/10954886.

16. Violari A, Lindsey JC, Hughes MD, et al. Nevirapine versus ritonavir-boosted lopinavir for HIV-infected children. *N Engl J Med*. 2012;366(25):2380-2389. Available at: https://pubmed.ncbi.nlm.nih.gov/22716976.

17. Babiker A, Castro nee Green H, Compagnucci A, et al. First-line antiretroviral therapy with a protease inhibitor versus non-nucleoside reverse transcriptase inhibitor and switch at higher versus low viral load in HIV-infected children: an open-label, randomised phase 2/3 trial. *Lancet Infect Dis*. 2011;11(4):273-283. Available at: https://pubmed.ncbi.nlm.nih.gov/21288774.

18. Ruel TD, Kakuru A, Ikilezi G, et al. Virologic and immunologic outcomes of HIV-infected Ugandan children randomized to lopinavir/ritonavir or nonnucleoside reverse transcriptase inhibitor therapy. *J Acquir Immune Defic Syndr*. 2014;65(5):535-541. Available at: https://pubmed.ncbi.nlm.nih.gov/24326597.

19. Palumbo P, Lindsey JC, Hughes MD, et al. Antiretroviral treatment for children with peripartum nevirapine exposure. *N Engl J Med*. 2010;363(16):1510-1520. Available at: https://pubmed.ncbi.nlm.nih.gov/20942667.

20. Kamya MR, Mayanja-Kizza H, Kambugu A, et al. Predictors of long-term viral failure among Ugandan children and adults treated with antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2007;46(2):187-193. Available at: https://pubmed.ncbi.nlm.nih.gov/17693883.

21. Lowenthal ED, Ellenberg JH, Machine E, et al. Association between efavirenz-based compared with nevirapine-based antiretroviral regimens and virological failure in HIV-infected children. *JAMA*. 2013;309(17):1803-1809. Available at: https://pubmed.ncbi.nlm.nih.gov/23632724.

22. Kekitiinwa A, Spyer M, et al. Virologic response to first-line efavirenz- or nevirapine-based antiretrovial therapy in HIV-infected African children. *Pediatr Infect Dis J*. 2017;36(6):588-594. Available at: https://pubmed.ncbi.nlm.nih.gov/28505015/

23. Giaquinto C, Anabwani G, Feiterna-Sperling C, et al. Steady-state pharmacokinetics of nevirapine extended-release tablets in HIV-1-infected children and adolescents: an open-label, multiple-dose, cross-over study. *Pediatr Infect Dis J*. 2014;33(7):e173-179. Available at: https://pubmed.ncbi.nlm.nih.gov/24378938.

24. Anabwani G, Konigs C, Giaquinto C, et al. Nevirapine extended-release formulation tablets in HIV-1-infected children--long-term follow-up. *Clin Infect Dis*. 2015;61(3):476-479. Available at: https://pubmed.ncbi.nlm.nih.gov/25917636.

25. Havlir D, Cheeseman SH, McLaughlin M, et al. High-dose nevirapine: safety, pharmacokinetics, and antiviral effect in patients with human immunodeficiency virus infection. *J Infect Dis*. 1995;171(3):537-545. Available at: https://pubmed.ncbi.nlm.nih.gov/7533197.

26. Mulenga V, Cook A, Walker AS, et al. Strategies for nevirapine initiation in HIV-infected children taking pediatric fixed-dose combination "baby pills" in Zambia: a randomized controlled trial. *Clin Infect Dis*. 2010;51(9):1081-1089. Available at: https://pubmed.ncbi.nlm.nih.gov/20868279.

27. Fillekes Q, Mulenga V, Kabamba D, et al. Is nevirapine dose escalation appropriate in young, African, HIV-infected children? *AIDS*. 2013;27(13):2111-2115. Available at: https://pubmed.ncbi.nlm.nih.gov/23595153.

28. Magnusson MO, Dahl ML, Cederberg J, et al. Pharmacodynamics of carbamazepine-mediated induction of CYP3A4, CYP1A2, and Pgp as assessed by probe substrates midazolam, caffeine, and digoxin. *Clin Pharmacol Ther*. 2008;84(1):52-62. Available at: https://pubmed.ncbi.nlm.nih.gov/17971810.

29. Ruel TD, Capparelli EV, Tierney C, et al. Pharmacokinetics and safety of early nevirapine-based antiretroviral therapy for neonates at high risk for perinatal HIV infection: a phase 1/2 proof of concept study. *Lancet HIV*. 2020;S2352-3018(20):30274-30275. Available at: https://pubmed.ncbi.nlm.nih.gov/33242457.

30. Bekker A, Hanan N, Violari A, et al. Population pharmacokinetics of nevirapine in preterm infants and prediction of doses needed for treatment in combination with other antiretrovirals. . Presented at: 11th International Workshop on HIV Pediatrics; 2019. Mexico City, Mexico. Available at: https://www.impaactnetwork.org/ias-2019.

31. Maswabi K, Ajibola G, Bennett K, et al. Safety and efficacy of starting antiretroviral therapy in the first week of life. *Clin Infect Dis*. 2020;ciaa02. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31927562.

32. Ajibola G, Maswabi K, Hughes MD, et al. Brief Report: Long-Term Clinical, Immunologic, and Virologic Outcomes Among Early-Treated Children With HIV in Botswana: A Nonrandomized Controlled Clinical Trial. *J Acquir Immune Defic Syndr*. 2023;92(5):393-398. Available at: https://pubmed.ncbi.nlm.nih.gov/36729692.