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Research Article

# Clinical pharmacology of lamivudine administered alone, or co-administered with other antiviral drugs, in infants and children

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- Placenta
- Breast-milk
- Infants and children

**Abstract**

Lamivudine is a cytidine analogue reverse transcriptase inhibitor that is active against HIV-1, HIV-2, and HBV; it is approved for HIV in adults and in children aged 3 months or older. Lamivudine enter cells by passive diffusion and is phosphorylated to lamivudine 5'-triphosphate which is the active anabolite. Lamivudine is administered orally, its oral bioavailability is 86%, and lamivudine is primarily excreted unchanged in the urine. Lamivudine may be administered alone but in most cases it is co-administered with other antiviral drugs. The oral dose of lamivudine is 4 mg/kg twice-daily in infants, and in children it is computed according to the child age and body-weight and the maximum dose is 300 mg once-daily. Lamivudine co-administered with antiviral drugs has been found efficacy and safe in infants and children with HIV-infection and lamivudine prevents the transmission of hepatitis B virus from mother-to-infant. Lamivudine elimination half-life is about 6 hours in infants and about 4 hours in infants and children. The prophylaxis and treatment with lamivudine have been studied in infants and children. The prophylaxis and treatment often consist in lamivudine co-administered with other antiviral drugs such as nevirapine, lopinavir/ritonavir or zidovudine. Lamivudine freely crosses the human placenta and freely migrates into the breast-milk. The aim of this study is to review the lamivudine dosing, efficacy, safety, prevention of mother-to-infant transmission of hepatitis B virus, pharmacokinetics, interaction with drugs, prophylaxis, and treatment in infants and children, the transfer across the human placenta and the migration into the breast-milk.

## INTRODUCTION

Lamivudine (3TC) is a cytidine analogue reverse transcriptase inhibitor that is active against HIV-1, HIV-2 (HIV: human immunodeficiency virus), and HBV (hepatitis B virus). Lamivudine is approved for HIV in adults and children aged 3 months or older. Lamivudine has been effective in combination with other antiretroviral drugs in both treatment-naïve and -experienced patients and is a common component of therapy, given its safety, convenience, and efficacy. Lamivudine is also approved for treatment of chronic HBV infection [1].

### Mechanism of action of lamivudine

Lamivudine enter cells by passive diffusion and is sequentially phosphorylated to lamivudine 5'-triphosphate which is the active anabolite. Lamivudine has low affinity for human DNA polymerase, explaining its low toxicity to the host. High-level resistance to lamivudine occurs with single-amino-acid substitutions, M184V or M184I. These mutations can reduce in-vitro sensitivity to lamivudine as much as 1,000-fold. The M184V mutation restores the susceptibility in zidovudine-resistant HIV harbouring the K65R mutation. The effect may contribute to the sustained virological benefits of zidovudine and lamivudine combination therapy [1].

### Absorption distribution metabolism and excretion of lamivudine

The oral bioavailability of lamivudine is 86% and the food does not affect the bioavailability of lamivudine. In adults, the elimination half-life is 1.1 hours and that of lamivudine 5'-triphosphate is 12 hours. Lamivudine binds to plasma protein to < 35%, is metabolized at a rate < 36% and the renal excretion of lamivudine is 71%. Lamivudine is excreted primarily unchanged in the urine; dose adjustment is recommended in patients with a creatinine clearance < 50 ml/min. Lamivudine freely crosses the placenta and it is transferred to the foetal circulation [1].

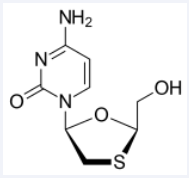

**Figure 1** Molecular structure of lamivudine (molecular weight = 229.26 grams/mole).

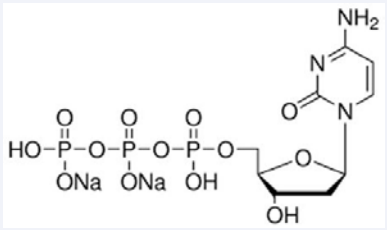

**Figure 2** Molecular structure of lamivudine 5′-triphosfate disodium salt (molecular weight = 490.15 grams/mole).

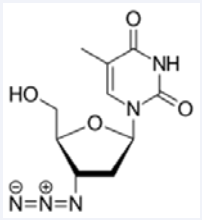

**Figure 3** Zidovudine molecular structure (molecular weight = 267.242 grams/mole).

### Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "lamivudine dosing infants, children", lamivudine efficacy, safety infants, children", "lamivudine pharmacokinetics infants, children", "lamivudine drug interactions", "lamivudine prophylaxis infants, children", "lamivudine treatment infants, children", "lamivudine placental transfer", and "lamivudine migration into the breast-milk". In addition, the books: The Pharmacological Basis of Therapeutics [1], Neonatal Formulary [2], NEOFAX® by Young and Mangum [3], and The British National Formulary for Children [4] were consulted.

## RESULTS

### Administration schedules of lamivudine to infants and children

**Oral administration to infants** [2]

**Infants:** Give: 4 mg/kg twice-daily alone or combined with two or more antiviral drugs. In the rare situations where treatment is called for the first month of life give 2 mg/kg twice-daily.

Prevention of mother-to-infant HIV transmission in infants born to HIV-infected women who have had received no therapy during pregnancy (has received intrapartum therapy only) in combination with zidovudine. The use of lamivudine with zidovudine for 7 days postpartum is an alternative regimen according to WHO guidelines. The decision to use combination infant antiretroviral prophylaxis, or the treatment of infected infants with combination antiretroviral therapy, should be done in consultation with a paediatric infectious disease expert [3].

**Oral treatment to children** [4]

**Oral treatment of HIV-infection in combination with other antiretroviral drugs using Epivir® oral solution**

**Children aged 1 to 2 months.** Give: 4 mg/kg twice-daily.

**Children aged 3 months to 11 years with body-weight up to 14 kg.** Give: 4 mg/kg twice-daily (maximum dose = 150 mg), alternatively give: 8 mg/kg once-daily (maximum dose = 300 mg).

**Children aged 3 months to 11 years with body-weight of 14 to 20 kg.** Give: 4 mg/kg twice-daily (maximum dose = 150 mg), alternatively 8 mg/kg once-daily (maximum dose = 300 mg), alternatively 75 mg twice-daily, alternatively 150 mg once-daily.

**Children aged 3 months to 11 years with body-weight of 21 to 29 kg.** Give: 4 mg/kg twice-daily (maximum dose = 150 mg), alternatively 8 mg/kg once-daily (maximum dose = 300 mg), alternatively 75 mg/kg daily and the dose should be taken in the morning and 150 mg should be taken in the evening, alternatively the dose is 225 mg once-daily.

**Children aged 3 months to 11 years with body-weight ≥ 30 kg.** Give: 4 mg/kg twice-daily (maximum dose = 150 mg), alternatively 8 mg/kg once-daily (maximum dose = 300 mg), alternatively 300 mg once-daily, alternatively 150 mg twice-daily.

**Children aged 12 to 17 years.** Give: 150 mg twice-daily, alternatively 300 mg once-daily.

Oral treatment of HIV-infection in combination with other antiviral drugs using Epivir® tablets

**Children aged 1 to 2 months.** Give: 4 mg/kg twice-daily.

**Children aged 3 months to 11 years with body-weight up to 14 kg.** Give: 4 mg/kg twice-daily (maximum dose = 150 mg), alternatively 8 mg/kg once-daily (maximum dose = 300 mg).

**Children aged 3 months to 11 years with body-weight of 14 to 20 kg.** Give: 4 mg/kg twice-daily (maximum dose = 150 mg), alternatively 8 mg/kg once-daily (maximum dose = 300 mg), alternatively 75 mg twice-daily, alternatively 150 mg once-daily.

**Children aged 3 months with body-weight of 21 to 29 kg.** Give: 4 mg/kg twice-daily (maximum dose = 150 mg), alternatively 8 mg/kg once-daily (maximum dose = 300 mg), alternatively 75 mg daily and the dose should be taken in the morning and 150 mg should be taken in the evening, alternatively 225 mg once-daily.

**Children aged 3 to 11 years with body-weight ≥ 30 kg.** Give: 4 mg/kg twice-daily (maximum dose = 150 mg), alternatively 8 mg/kg once-daily (maximum dose = 300 mg), alternatively 150

mg twice-daily, alternatively 300 mg once-daily.

**Children aged 12 to 17 years. Give:** 150 mg twice-daily, alternatively 300 mg once-daily.

Oral treatment of chronic hepatitis B infection either with compensated liver disease (with evidence of viral replication and history of active liver inflammation or fibrosis) when the first-line treatments cannot be used, or (in combination with another antiviral drug without cross-resistance to lamivudine) with decompensated liver cirrhosis using Zeffix®.

**Children aged 2 to 11 years.** Give: 3 mg/kg once-daily (maximum dose = 100 mg), children receiving lamivudine for concomitant HIV-infection should continue to receive lamivudine in a dose appropriate for HIV-infection.

**Children aged 12 to 17 years.** Give: 100 mg once-daily, children receiving lamivudine for concomitant HIV-infection should continue to receive lamivudine in a dose appropriate for HIV-infection.

Epivir® oral solution and tablets and Zeffix® are British formulations.

**Efficacy and safety of lamivudine co-administered with other antiviral drugs in infants and children**

Treatment with nevirapine plus zidovudine and lamivudine started in the first week of life is efficacy and safe, even when the trough concentration of nevirapine is below the target value. Transient HIV increases occur following transmission to lopinavir/ritonavir but at 12 and 24 weeks of treatment most infants achieved and maintained viral suppression [5]. Lamivudine co-administered with zidovudine is safe and effective in preventing maternal-to-infant HIV transmission [6]

Zidovudine plus lamivudine, lopinavir/ritonavir was found efficacy and safe in children with HIV-infection [7].

## Efficacy and safety of lamivudine administered alone or co-administered with other antiviral drugs in preventing the mother-to-infant transmission of hepatitis B virus

Lamivudine treatment of highly hepatitis B infection in pregnant women decreases the perinatal transmission of hepatitis B virus and lowers the infection caused by this virus in newborn infants [8]. Lamivudine prevents the maternal-to-infant hepatitis B virus transmission and reduces the complications caused by this virus in pregnant women and their newborn infants [9]. Continuous antiviral therapy with lamivudine from preconception to entire pregnancy is effective and safe for treatment of chronic hepatitis B virus in mothers and their newborn infants [10]. Lamivudine is efficacy and safe in preventing the transmission of hepatitis B virus from the mothers to their newborn infants [11]. Lamivudine treatment in hepatitis B virus carrier-mothers from 28 week of gestation interrupts the mother-to-infant transmission of hepatitis B virus. Lamivudine is safe and more efficient than hepatitis B immunoglobulin in interrupting mother-to-infant transmission of hepatitis B virus [12]. Lamivudine in hepatitis B virus carrier-mothers with high degree of infectiousness in late pregnancy effectively prevents

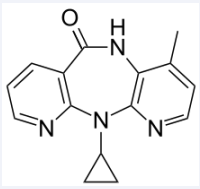

**Figure 4** Molecular structure of nevirapine (molecular weight = 266.298 grams/mole).

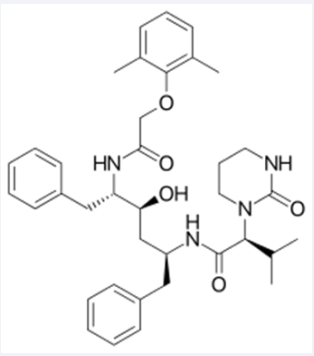

**Figure 5** Lopinavir molecular structure (molecular weight = 628.814 grams/mole).

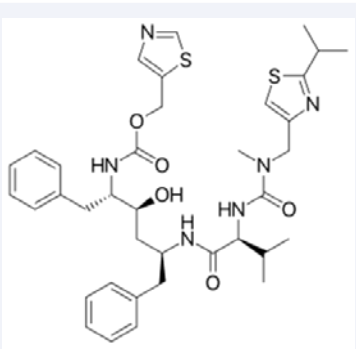

**Figure 6** Ritonavir molecular structure (molecular weight = 720.948 grams/mole).

hepatitis B virus intrauterine infection and the maternal-to-infant transmission [13]. Lamivudine therapy is efficacious and safe in infants with chronic hepatitis B [14]. Lamivudine and telbivudine treatment initiated in the third trimester of pregnancy for mothers with hepatitis B DNA > $1*10^6$ IU/ml is efficacy and safe in preventing the transmission of hepatitis B virus from mothers to their newborn infants [15].

Both lamivudine and tenofovir exhibited a high efficacy in preventing the transmission of the hepatitis B virus from the mothers to their newborn infants [16].

## Pharmacokinetics of lamivudine in infants

Mirochnick et al. [17] studied the pharmacokinetics of lamivudine in 26 infants during the first two weeks of life. Fourteen infants were aged 4 to 7 days and 12 infants were aged 10 to 14 days. The median gestational age is 39 weeks

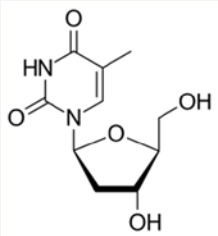

**Figure 7** Telbivudine molecular structure (molecular weight = 242.23 grams/mole)
A high efficacy in preventing the transmission of the hepatitis B virus from the mothers to their newborn infants [16].

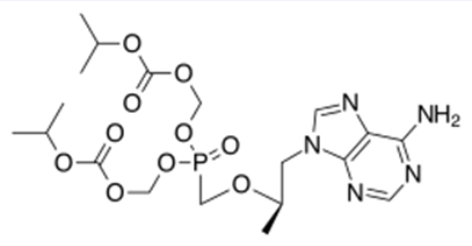

**Figure 8** Tenofovir molecular structure (molecular weight = 287.213 grams/mole).

(range, 34 to 42) and body-weight is 3,105 grams (range, 1,775 to 3,900). The median HIV viral load is 8,622 copies/ml (range, 224 to 53,773), and a median CD4 cell count is 704 cells/$mm^3$ (range, 143 to 1,711). Infants were treated with nelfinavir at a median dose of 58.8 mg/kg (range, 48.7 to 79.0) and lamivudine at a median dose of 2.0 mg/kg (range, 1.5 to 3.2). Nelfinavir and lamivudine were administered orally twice-daily. [Table 1]

This table shows that the elimination half-life is the only pharmacokinetic parameter that differs in the two groups of infants and it is shorter in infants aged 10 to 14 days than in infants aged 4 to 7 days.

## Pharmacokinetics of lamivudine in infants and children

Tremoulet et al. [18] investigated the pharmacokinetics of lamivudine in 99 HIV-exposed infants and children aged 56±163 days (range, 3 to 757) and weighing 4.2±2.7 kg (range, 2.1 to 16.2). Lamivudine was administered orally at a dose of 2 to 4 mg/kg twice-daily. Further information about lamivudine dosing is included in [Table 2].

This table shows that the total body clearance, corrected for the oral bioavailability, is greater in children than in infants. The distribution volume is not different in infants and children and it is greater than the water volume. The elimination half-life is longer in infants than in infants and children, the AUC is similar in infants and children and there is a wide interindividual variability in the pharmacokinetic parameters.

## Pharmacokinetics of lamivudine administered alone or co-administered with zidovudine in newborn infants

Moodley et al. [19] explored the pharmacokinetics of lamivudine administered alone or co-administered with zidovudine in twenty pregnant women infected by HIV-1 and in their offspring. Ten women received 4 mg/kg of lamivudine and 10 women were treated with lamivudine at a dose of 150 mg plus zidovudine at a dose of 300 mg and both drugs were administered orally twice-daily during the first week before delivery and intrapartum. Ten newborn infants received lamivudine at a dose of 4 mg/kg twice-daily and 10 newborn infants received this dose of lamivudine plus 2 mg/kg zidovudine 4 times-daily orally. Lamivudine and zidovudine were administered orally. [Table 3]

This table shows that zidovudine causes a modest reduction of AUC and peak concentration of lamivudine.

Bergshoeff et al. [20] studied the pharmacokinetics of lamivudine in 19 HIV-1-infected children aged 2 to 13 years who were clustered into two groups according to the age. Then children of group A were aged ≥ 2 to 6 years, and 9 children of group B were aged > 6 to 13 years. The oral dose of lamivudine was 4 mg/kg twice-daily or 8 mg/kg once-daily (Table 4).

This table shows that the minimum concentration of lamivudine is the only pharmacokinetic parameter which is different in the two groups of children.

## Interaction of lamivudine with drugs

Lamivudine dolutegravir interaction is particularly relevant because increase the risk of toxicity in patients with HIV [21].

Lamivudine is a substrate of renal drug transporters OCT2, MATE1, and MATE2-K and concomitant administration of drugs

**Table 1.** Pharmacokinetic parameters which are obtained in 13 infants aged 4 to 7 days and in 12 infants aged 10 to 14 days. Figures are the median and (range), by Mirochnick et al [17].

| Parameter | Age 4 to 7 days (N = 13) | Age 10 to 14 days (N = 12) | Combined age groups (N = 25) |
|---|---|---|---|
| Tmax (h) | 2.8 (1 – 4) | 2.5 (1 – 4) | 2.5 (1 – 4) |
| Peak concentration (µg/ml) | 1.08 (0.38 – 2.01 | 1.27 (0.38 – 2.17) | 1.24 (0.38 – 2.17) |
| Concentration at 12 hours (µg/ml) | 0.31 (bql – 0.74) | 0.22 (bql – 0.62) | 0.23 (bql – 0.74 |
| $AUC_{0\text{-}12\,h}$ (µg*h/ml) | 7.0 (2.9 – 15.6) | 7.9 (2.7 – 14.0) | 7.8 (2.4 – 15.6) |
| Total body clearance/F (L/h/kg) | 0.27 (0.11 – 0.70) | 0.27 (0.14 – 0.74) | 0.27 (0.11 – 0.74) |
| Elimination half-life (h) | 5.3 (3.3 – 10.5) | 3.9 (3.1 – 6.3)* | 4.3 (3.1 – 10.5) |

Tmax = time to reach the peak concentration. F = oral bioavailability. bql = below quantification limit. *P-value < 0.05 (Student t test for unpaired data).

**Table 2.** Comparison of lamivudine pharmacokinetic parameters in HIV-infected infants and children. Figures are the median and (interquartile range), by Tremoulet et al. [18].

| Age group (sample size) | Oral dose (twice-daily) | Pharmacokinetic parameter: median and 95% confidence interval | | | |
|---|---|---|---|---|---|
| | | TBC/F (L/h/kg) | DV/F (L/kg) | *Half-life (h) | $AUC_{0\text{-}12\,h}$ (μg*h/ml) |
| 3-26 days (N = 40) | 2 mg/kg | 0.37 (0.25 – 0.48) | 3.12 (2.29 – 3.96) | 6.2 (4.6 – 7.8) | 6.0 (4.0 – 8.0) |
| 1 day (N = 16) | 2 mg/kg | 0.19 (0.14 – 026) | NA | 6.2 (5.3 – 8.0) | 9.8 (7.6 – 14.1) |
| 7 days (N = 16) | 2 mg/kg | 0.32 (0.26 – 40) | NA | 7.9 (7.0 – 9.0) | 6.3 (5.0 – 7.8) |
| 29 days-3 years (N = 59) | 4 mg/kg | 0.66 (0.46 – 0.86) | 3.44 (2.53 – 4.35) | 3.8 (2.8 – 4.8) | 6.8 (3.9 – 9.7) |

TBC = total body clearance. F = oral bioavailability. DV = distribution volume. NA = not available. *Elimination half-life.

**Table 3.** Pharmacokinetic parameters which are obtained in 10 newborn infants who received 4 mg/kg lamivudine twice-daily and in 10 newborn infants who received this dose of lamivudine plus 2 mg/kg zidovudine 4 times-daily. Figures are the geometric least squire (95% confidence interval), by Moodley et al. [19].

| | Lamivudine | | |
|---|---|---|---|
| **Parameter** | **Monotherapy** | **With zidovudine** | **Comparison** |
| $AUC_{\Omega}$ (μg/h/ml) | 16.88 (13.4 – 21.3) | 15.63 (12.4 – 19.7) | 1.07 (0.85 – 1.33) |
| Peak conc. (μg/ml) | 1.97 (1.6 – 2.3) | 1.69 (1.3 – 2.2) | 1.17 (0.91 – 1.49) |
| Tmax (h) | 3.0 (1.0 – 8.0) | 3.0 (1.0 – 3.0) | --- |
| TBC/F (L/h) | 1.1 (0.9 – 1.3) | 1.2 (0.8 – 1.6) | 0.90 (0.71 – 1.14) |
| Elimination half-life (h) | 6.0 (5.1 – 6.8) | 6.6 (5.3 – 7.9) | 0.90 (0.76 – 1.07) |

$AUC_{\Omega}$ = Ω is the dosing interval. TBC = total body clearance. F = oral bioavailability. Tmax = the time to reach the lamivudine peak concentration.

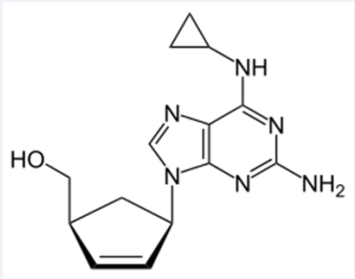


**Figure 9** Abacavir molecular structure (molecular weight = 286.332 grams/mole).

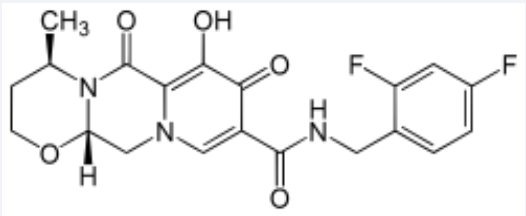


**Figure 10** Dolutegravir molecular structure (molecular weight = 419.38 grams/mole)

Lamivudine is a substrate of renal drug transporters OCT2, MATE1, and MATE2-K and concomitant administration of drugs that inhibit these transporters decrease the renal clearance of lamivudine [22]. Trimethoprim-sulfamethoxazole increases the lamivudine plasma concentrations by 43% [23].

that inhibit these transporters decrease the renal clearance of lamivudine [22]. Trimethoprim-sulfamethoxazole increases the lamivudine plasma concentrations by 43% [23].

## Prophylaxis with lamivudine in infants and children

The prophylaxis of infants infected by HIV-1 with lopinavir/ritonavir is not superior to that with lamivudine and both drugs led to very low rates of HIV-1 postnatal transmission for up to 50 weeks of breastfeeding [24]. The prophylaxis with lopinavir/ritonavir or with lamivudine prevents the HIV-1-infection in infants [25]. The prophylaxis with zidovudine/lamivudine or with didanosine prevents HIV-1-infection in children [26]. Zidovudine plus lamivudine and lopinavir/ritonavir prevents the HIV-1-infection in children [27].

## Treatment with lamivudine in infants and children

Among infants with prior exposure to single-dose nevirapine for perinatal prevention of HIV transmission, antiretroviral treatment consisting in zidovudine and lamivudine plus ritonavir/lopinavir results in better outcomes than does the treatment with zidovudine and lamivudine plus nevirapine [28]. Less weight gain is observed in infants given lopinavir/ritonavir than those given lamivudine, which is indicative of a persistent effect that could have long-term deleterious effects [29]. Reduction of viremia by lamivudine therapy in the last month of pregnancy is an effective and safe measure to reduce the risk of hepatitis B virus in newborn infants [30]. Children exposed to lopinavir/ritonavir and lamivudine at birth for 1

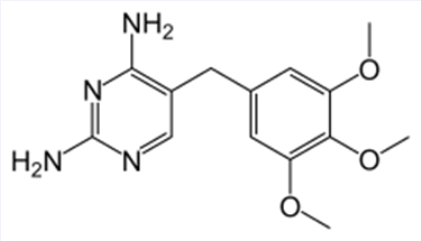

**Figure 11** Sulfamethoxazole molecular structure (molecular weight = 253,279 grams/mole).

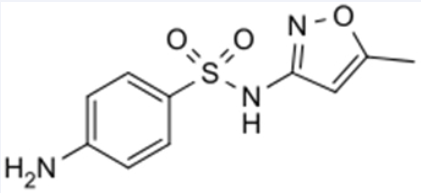

**Figure 12** Sulfamethoxazole molecular structure (molecular weight = 253,279 grams/mole).

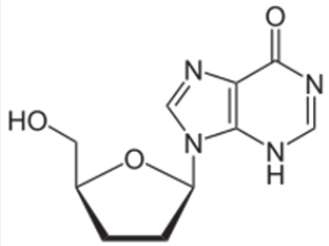

**Figure 13** Didanosine molecular structure (molecular weight = 236.2273 grams/mole).

year have comparable growth and neuropsychological outcomes without evidence of long-term side-effects [31]. Lamivudine monotherapy should be administered temporarily while efforts to improve adherence are implemented. Lamivudine should not be considered a default option in children with virological failure [32]. One year lamivudine therapy for children with chronic hepatitis B virus is effective and well tolerated treatment [33]. Lamivudine, administered in combination with zidovudine, is now established as an effective agent for the treatment of antiretroviral drug-experienced or -naïve children with asymptomatic or symptomatic HIV disease [34]. Lamivudine is well tolerated and exhibited virological activity in children, although future use in children is likely to be in combination antiretroviral regimens [35].

### Transfer of lamivudine across the human placenta

The placental transfer of lamivudine expressed as fetal to maternal AUC ratio is 0.86, and the lamivudine amniotic fluid accumulation, expressed as the amniotic fluid to fetal AUC ratio, is 2.9 [36]. The ratio between cord to maternal plasma for lamivudine is 0.93 [37]. Lamivudine crosses the placenta by simple diffusion and is concentrated in the amniotic fluid [38].

### Migration of lamivudine into the breast-milk

Waitt et al. [39] studied the pharmacokinetics of lamivudine in the maternal plasma and in breast-milk of 30 Ugandan and 29 Nigerian lactating women who received lamivudine at doses of 150 mg twice-daily or 300 mg once-daily [Table 5]

This table shows that lamivudine freely migrates into the breast-milk as the lamivudine $AUC_{0\text{-}12\ h}$ is similar in the breast-milk and in the maternal plasma.

Lamivudine was administered to 40 women from the 28$^{th}$ weeks of gestation to 1 month postpartum and the mean milk to plasma ratio of lamivudine is 1.8 [40]. Twenty lactating women were treated with lamivudine and the median concentration of lamivudine in the breast-milk to plasma ratio is 3.34 [41].

## DISCUSSION

Lamivudine (3TC) is a cytidine analogue reverse transcriptase inhibitor that is active against HIV-1, HIV-2 (HIV: human immunodeficiency virus), and HBV (hepatic B virus). Lamivudine is approved for HIV in adults and children aged 3 months or older. Lamivudine has been effective in combination with other antiretroviral drugs in both treatment-naïve and -experienced patients. Lamivudine enter cells by passive diffusion and is sequentially phosphorylated to lamivudine 5'-triphosphate which is the active anabolite. Lamivudine is administered orally and the oral bioavailability is 86%. In adults, the elimination half-life of lamivudine is 1.1 hours, that of lamivudine 5'-triphosphate

**Table 4.** Lamivudine pharmacokinetic parameters which are obtained in two groups of children. Figures are the geometric mean, (90% confidence interval), and P-values, by Bergshoeff et al. [20].

| | Lamivudine 4 mg/kg twice-daily | | | Lamivudine 8 mg/kg once-daily | | |
|---|---|---|---|---|---|---|
| **Parameter** | **10 Children of group A** | **9 Children of group B** | ***P-value** | **10 Children of group A** | **9 Children of group B** | ***P-value** |
| Body-weight (kg) | 16.0 12.5-29.3) | 26 (21.3-60.5) | NA | 16.1 (13.5-28.6) | 25.8 (22.2-61.3) | NA |
| Dose mg/kg | 4.1 (3.6-4.4) | 4.0 (2.5-4.9) | 0.54 | 8.3 (7.4-8.5) | 7.8 (4.9-9.3) | 0.65 |
| $AUC_{0\text{-}24\ h}$ (µg*h/ml) | 7.60 (6.12-9.45) | 10.5 (882-12.63) | 0.05 | 8.80 (7.43-10.34) | 11.04 (9.06-13.4) | 0.12 |
| Peak conc. (µg/ml) | 0.94 (0.78-1.13) | 1.34 (1.08-1.67) | 0.03 | 1.72 (1.48-1.99) | 2.59 (2.04-3.28) | 0.01 |
| Cmin (µg/ml) | 0.068 (<0.05-0.15) | 0.037 (<0.050-0.11) | NA | 0.050 (<0.050-0.076) | 0.061 (<0.050-0.074) | NA |
| TBC/F (L/h/kg) | 1.09 (0.89-1.34) | 0.73 (0.63-0.85) | 0.13 | 0.92 (0.78-1.08) | 0.69 (0.55-0.87) | 0.07 |

TBC = total body clearance. F = oral bioavailability. NA = not available. Cmin = lamivudine minimum concentration. *Student t test for unpaired data.

**Table 5.** Pharmacokinetic parameters of lamivudine which are obtained in the maternal plasma and in the beast-milk of 30 Ugandan and 29 Nigerian lactating women. Figures are the median and (interquartile range), by Waitt et al. [39]

| | Estimated values in plasma | | | Estimated values in breast-milk | | | |
|---|---|---|---|---|---|---|---|
| **Dose** | **Tmax (h)** | **Peak conc. (µg/ml)** | **$AUC_{0\text{-}12\ h}$ (µg*h/ml)** | **Tmax (h)** | **Peak conc. (µg/ml)** | **$AUC_{0\text{-}12\ h}$ (µg*h/ml)** | **$AUC_{0\text{-}12\ h}$ Milk/plasma ratio** |
| 150 mg twice-daily | 4 (2 – 4) | 0.64 (0.64 – 0.75) | 3.34 (2.82 – 3.74) | 6 (4 – 6) | 0.91 (0.77 -1.10) | 5.94 (5.26 – 6.13) | 1.65 (1.59 – 1.92) |
| 300 mg once-daily | 2 (1.5 – 3) | 0.91 (0.63 – 1,11) | 4.54 (3.16 – 5.99) | 6 (4 – 8) | 0.63 (0.44 – 0.89) | 4.42 (2.11 – 5.50) | 0.95 (0.82 – 1.15) |

is 12 hours, and lamivudine is primarily eliminated unchanged in the urine [1]. The oral dose of lamivudine is 4 mg/kg twice-daily in infants and it may be administered alone or combined with two or more antiviral drugs [2]. In children, the oral dose of lamivudine is computed according to the child age and the body-weight and the maximum dose is 300 mg once-daily [4]. Lamivudine has been found efficacy and safe in infants and children even when it is combined with other antiviral drugs [5-7]. The treatment with lamivudine plus nevirapine and zidovudine has been found efficacy and safe in infants with HIV-infection [5], and lamivudine co-administered with zidovudine is safe and effective in preventing maternal-to-infant HIV transmission [6]. Lamivudine plus zidovudine and lopinavir/ritonavir is efficacy and safe in children with HIV-infection [7]. Lamivudine prevents the transmission of hepatitis B virus from mother-to-infant [8-16]. Lamivudine decreases the transmission of hepatitis B virus from the mothers to their newborn infants [8-13], lamivudine therapy is efficacious and safe in infants with chronic hepatitis B infection [14], the treatment with lamivudine and telbivudine [15] or lamivudine plus tenofovir [16] prevents the transmission of hepatitis B virus from infected mothers to their newborn infants. The median elimination half-life of lamivudine is about 6 in infants and 4 hours in infants and children [17-18]. The total body clearance is lower in infants than in infants and children, the distribution volume is about 3 L/kg in these infants and children and it is not affected by infant maturation and child development [18]. The co-administration of zidovudine with lamivudine causes modest effects on the pharmacokinetic parameters of lamivudine [19]. Lamivudine administered at a dose of 4 mg/kg twice-daily or at a dose of 8 mg/kg once-daily produces similar pharmacokinetic parameters with the exception of the total body clearance which is higher following a dose of 8 mg/kg once-daily [20]. Lamivudine interacts with drugs [21-23]. Dolutegravir co-administered with lamivudine increase the risk of toxicity [21], the renal clearance of lamivudine is decreased when lamivudine is co-administered with drugs that inhibit the renal transport [22], and trimethoprim-sulfamethoxazole increases the plasma concentration of lamivudine [23]. The prophylaxis with lamivudine has been described in infants and children [24-27]. The prophylaxis of infants infected by HIV-1 with lopinavir/ritonavir is not superior to that with lamivudine and prevents the HIV-1-infection in infants [24-25]. The prophylaxis with zidovudine plus lamivudine or with didanosine [26] and that with zidovudine plus lopinavir/ritonavir and lamivudine [27] prevents HIV-1-infection in children. The treatment with zidovudine has been studied in infants and children [28-35]. The treatment with lamivudine plus zidovudine and lopinavir/ritonavir successfully treated infants with HIV-infection [28], treatment with lopinavir/ritonavir is superior to that with lamivudine [29], and lamivudine treatment reduces the risk of hepatitis B virus in newborn infants [30]. Children exposed to lopinavir/ritonavir or to lamivudine produce comparable growth and neuropsychological outcomes without evidence of adverse-effects [31]. Lamivudine monotherapy should be administered temporarily and should be considered a default option in children with virological failure [32] and lamivudine administered for one year is effective and well tolerated in children with Hepatitis B virus infection [33]. Lamivudine plus zidovudine is an effective treatment in children with HIV disease [34]. The treatment with lamivudine in children exhibits virological activity but the combination of lamivudine with antiretrovirals dugs is preferred [35]. Lamivudine freely crosses the human placenta [23-38] and freely migrates into the breast-milk [39-41].

In conclusion, lamivudine is a cytidine analogue reverse transcriptase that is active against HIV-1, HIV-2 and HBV. Lamivudine is approved for HIV in adults and children aged 3 months or older, but lamivudine is often co-administered with other antiviral drugs. Lamivudine is converted into lamivudine 5'-triphosphate which is the active anabolite. Lamivudine is administered orally, the oral bioavailability is 86%, and lamivudine is primarily eliminated in the urine. The oral dose of lamivudine is 4 mg/kg twice-daily in infants, and in children it is computed according to the child age and body-weight and the maximum dose is 300 mg once-daily. Lamivudine co-administered with other antiviral drugs has been found efficacy and safe in infants and children with HIV-infection and prevents the transmission of hepatitis B virus from infected mothers to their newborn infants. The elimination half-life of lamivudine is about 6 hours in infants and it is about 4 hours in infants and children. The prophylaxis and the treatment with lamivudine have been extensively investigated in infants and children. Lamivudine freely crosses the human placenta and freely migrates into the breast-milk. The aim of this study is to review the clinical pharmacology of lamivudine in infants and children.

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