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Pharmacokinetics and Antiretroviral Activity of Lamivudine Alone or When Coadministered with Zidovudine in Human Immunodeficiency Virus Type 1–Infected Pregnant Women and Their Offspring


The safety, pharmacokinetics, and antiretroviral activity of lamivudine alone and in combination with zidovudine was studied in pregnant women infected with human immunodeficiency virus type 1 (HIV-1) and their neonates. Women received the drugs orally from week 38 of pregnancy to 1 week after delivery. Neonate therapy began 12 h after delivery and continued for 1 week. Both treatment regimens were well-tolerated in women and newborns. Lamivudine and zidovudine pharmacokinetics in pregnant women were similar to those in nonpregnant adults. Lamivudine and zidovudine freely crossed the placenta and were secreted in breast milk. Neonatal lamivudine clearance was about half that in pediatric patients; zidovudine clearance was consistent with previous reports. HIV-1 RNA could be quantified in 17 of the 20 women. At the onset of labor/delivery, mean virus load had decreased by \(-1.5\) log\(_{10}\) copies/mL in both treatment cohorts. Although not definitive for HIV-1 infection status, all neonates had HIV-1 RNA levels below the limit of quantification at birth and at ages 1 and 2 weeks.

In a placebo-controlled clinical trial in the United States and France (AIDS Clinical Trial Group [ACTG] 076) in subjects infected with human immunodeficiency virus type 1 (HIV-1), zidovudine given during pregnancy and delivery and to neonates substantially reduced the transmission of HIV-1 infection from 25.5% to 8.3% [1]. This regimen, however, is impractical in developing countries for a number of reasons. In ACTG 076, subjects received treatment from weeks 14–34 of gestation, whereas in developing countries, pregnant women often present at an antenatal clinic very late in pregnancy. Also, the cost of a lengthy regimen with an intravenous component during labor would be prohibitive in cost in this setting. Finally, ACTG 076 was conducted in a non-breast-feeding population. Given the risk of HIV-1 transmission through breast-feeding [2–4], the efficacy of the ACTG 076 regimen is unknown in a breast-feeding population.

In addition, because evidence suggests that most maternal-fetal HIV-1 transmission occurs late in pregnancy and during delivery [5, 6], a short, practical, and affordable regimen in a breast-feeding population needs to be investigated. The combination of lamivudine and zidovudine has an established safety profile in adults and children >3 months of age, and the safety of zidovudine has been established in neonates [7, 8]. Treatment in naive adults results in a 1.5 log\(_{10}\) reduction in virus load after 2 weeks [9]. The combination would therefore seem to be potentially useful in the prevention of maternal-fetal transmission, although there are no data on therapy with lamivudine-zidovudine combination therapy in pregnant women or neonates.

This study was designed to provide information on the safety and pharmacokinetics of lamivudine alone and in combination with zidovudine in pregnant women and their neonates. The data produced were to be used specifically to recommend lamivudine regimens on the basis of pharmacokinetic exposure for use in subsequent efficacy studies, including the Joint United Nations Programme on HIV/AIDS (UNAIDS)–sponsored perinatal transmission (PETRA) study. A further objective was to assess the antiviral activity of combined lamivudine and zidovudine in pregnant women, although this information was superseded by that from a subsequent efficacy study. Finally,
where sufficient sample volume remained after lamivudine bioanalysis, zidovudine concentrations were assessed for pharmacokinetic evaluation.

Materials and Methods

Subjects. Twenty pregnant HIV-1-positive women who were otherwise free of significant disease were enrolled in this study. Primary exclusion criteria were multiple pregnancies; pregnancy complications or anticipated elective cesarean section; significant laboratory abnormalities, including hemoglobin levels <8 g/dL before entry; and previous antiretroviral therapy. After delivery, the 20 neonates were enrolled in the study.

Design. This was a single center (Durban, South Africa), phase II, open-label, repeat-dose, randomized, two-way, parallel-group study. Two groups of 10 women received either lamivudine alone (300 mg twice daily) or lamivudine (150 mg twice daily) with zidovudine (300 mg twice daily) before delivery (from 38 weeks gestation), intrapartum, and for 1 week after delivery. At the onset of labor, the women received either a single 300-mg lamivudine dose or 150 mg of lamivudine with 300 mg of zidovudine orally. Lamivudine oral dosing was continued every 12 h during labor. Women assigned to combination therapy also were given 300 mg of zidovudine orally every 3 h until delivery. In the absence of any life-threatening condition or severe laboratory abnormality, neonates were treated for 1 week in accordance with their mother’s randomization, commencing 12 h after delivery. Neonates were given lamivudine orally—alone (4 mg/kg twice daily) or in combination with zidovudine (2 mg/kg 4 times/day).

Safety assessments. All women received full medical evaluations, and hematologic and biochemical analyses were done throughout the study. Clinical adverse events were monitored continuously with standard intrapartum fetal monitoring. Infants were examined postpartum and received regular clinical examinations to age 12 months. Neonates had hematologic and biochemical analyses to age 6 weeks.

Maternal sampling. Serum samples were analyzed initially to determine lamivudine concentrations and if sample volumes permitted, zidovudine concentrations were also determined. Blood samples were collected on day 1 of therapy (week 38 of gestation), before drug administration (predose), at 30 min and at 1, 2, 4, 8, and 12 h after drug administration (postdose), and at the start of labor and every 6 h thereafter. At birth, samples were obtained of maternal blood, amniotic fluid (when possible), and cord blood upon clamping. One week postpartum, a full profile (as on day 1) was collected with an additional 24-h postdose sample. Where possible, breast-milk samples (0.5–5 mL) were taken daily before feeding.

Neonatal sampling. Serum samples for determination of drug concentration were collected at birth (to coincide with the maternal sampling/cord clamping); at 1, 3, 8, and 12 h after birth; before therapy on days 6 and 7; and 1, 3, 8, 12, and 24 h postdose on day 7.

Serum, breast milk, and amniotic fluid samples were analyzed for lamivudine by a validated high-performance liquid chromatography method using UV detection [10]. The assay has a lower limit of quantification of 20 ng/mL. Serum and breast milk samples were analyzed for zidovudine by a validated RIA commercial kit (Zidovudine-Trac; IncStar, Stillwater, MN).

Pharmacokinetic and statistical analysis. The maximum drug concentration in serum (Cmax) and the time to Cmax (tmax) were determined directly from the concentration-time data. The terminal serum half-life (t1/2), area under the concentration-time curve (AUC), and oral clearance (CL/F) were calculated by model-independent analysis (WinNONLIN version 1.1; Scientific Consulting, Cary, NC). All analyses used SAS software (version 6.08; SAS, Cary, NC).

Antiretroviral activity. During the first day of drug therapy, maternal plasma samples for virologic analysis were obtained before treatment and at 4, 8, 12, and 24 h after therapy. Further samples were obtained during pregnancy and labor, at birth, and at 1 and 2 weeks after birth. Neonatal samples were collected at birth and at 1 and 2 weeks after birth. Quantitative polymerase chain reaction (PCR) was done on maternal and neonatal plasma (Amplicor; Roche Diagnostics, Nutley, NJ) [11]. The resulting PCR fragments were sequenced using the fluorescein sulphonate dye terminator kit (Applied Biosystems, Foster City, CA). Products were analyzed by automated DNA sequencer (model 373; Applied Biosystems).

Results

Patient Demographics

All women were 18- to 34-year-old black Africans. Three women in the group given combination therapy were CDC class B at entry; all others were CDC class A. Maternal and neonatal demographics in both groups were similar. The time between the first dose of drug(s) and birth varied widely (0–28 days) with a median of 13.7 days in the lamivudine group and 15.7 in the combination therapy group.

Safety

Both lamivudine and lamivudine plus zidovudine were well-tolerated. No woman or neonate discontinued treatment because of an adverse event, and no serious adverse events were considered related to study medication. In 1 mother given lamivudine monotherapy, hemoglobin declined from 7.8 g/dL at entry to 6.5 g/dL at delivery.

Two neonates died at ages 5 and 6 months during follow-up; neither death was considered related to study drug. Four neonates experienced serious adverse events; however, after investigation, these were not considered treatment-related: acute renal failure, meconium aspiration, gastroenteritis, and jaundice.

Two neonates had “nonserious” adverse events that may have been treatment-related. One neonate, who received combination therapy, had a rash on day 6 of therapy, which resolved in 2 days. Another, who received lamivudine alone, had mild anemia (hemoglobin: 9.1 g/dL) at age 6 weeks, which resolved. Other unrelated adverse events were mainly ear, nose, and throat and lower respiratory tract infections.
Pharmacokinetics

**Lamivudine.** Maternal pharmacokinetic parameter estimates for lamivudine at either week 38 of pregnancy (first dose) or after repeated twice-daily doses for 1 week after delivery (table 1, figure 1) showed no interaction between lamivudine and zidovudine. The lamivudine accumulation ratio following repeated twice-daily dosing ranged from 1 to 1.4 with a dominant elimination half-life of 5–7 h.

Mean concentrations of lamivudine in serum, amniotic fluid, and breast milk for lamivudine monotherapy were 550 ng/mL (range, 102–2520), 1.83 µg/mL (range, 1.2–2.5), and 1.22 µg/mL (range, <0.5–6.09), respectively. Similar results were recorded for lamivudine in the combination group: 301 ng/mL (range, 183–883), 3.85 µg/mL (range, 2.1–5.2), and 0.9 µg/mL (<0.5–8.2).

Following birth, the terminal elimination rate was similar between treatment groups (figure 2). The mean lamivudine elimination half-life (or washout) in neonates immediately after birth was 13.95 h (range, 6.2–35.1). Lamivudine concentrations for mother, cord blood, and the neonate at birth were very similar to therapeutic doses with maternal–cord blood–neonate ratios near unity. Median (range) times between last treatment dose and onset of labor for the combination group was 11.6 h (0.7–13.9) and 7.1 h (0.7–13.0) between last treatment dose and birth. The median (range) lamivudine concentration at the onset of labor in this treatment group was 165 ng/mL (range, 83–1150).

Lamivudine pharmacokinetics in neonates at age 1 week did not differ with or without zidovudine administration (table 2, figure 3). After twice-daily dosing for 1 week, lamivudine oral clearance in neonates was 0.4 L/h/kg.

**Zidovudine.** Zidovudine pharmacokinetic parameter estimates (Cmax, tmax, and t1/2) at week 38 of pregnancy (single dose) were 1607 ng/mL, 0.5 h, and 1.7 h, respectively. These parameters were similar to those calculated at postpartum week 1 (multiple dose). The AUC and CL/F for the single prepartum dose were 2533 ng/h/mL and 119 L/h, and both of these parameters differed significantly (P < 0.05) from the repeat postpartum steady-state dosing parameters: 4179 ng/h/mL and 72 L/h. The geometric least-squares mean ratios for AUC and CL/F were 1.65 and 0.61, respectively. Average zidovudine steady-state concentration after delivery was 357 ng/mL.

The median (range) concentration at the onset of labor was 20.23 ng/mL (11.32–324.67) before a 300-mg zidovudine loading dose: A loading dose was given if the preceding dose was

![Figure 1. Lamivudine and zidovudine (mean ± SD) serum concentration vs. time in pregnant women at week 38 of gestation after single oral dose: 300 mg of lamivudine (○), 150 mg of lamivudine + zidovudine (□), or 300 mg of zidovudine + lamivudine (△).](image)

### Table 1. Maternal prepartum (single dose) and postpartum (steady-state) lamivudine (LAM) pharmacokinetic parameters after oral dose of drug.

<table>
<thead>
<tr>
<th>Drug given</th>
<th>LAM monotherapy (300 mg twice/day)</th>
<th>LAM plus zidovudine (150 mg twice/day)</th>
<th>Comparison*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before delivery (first dose)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AUC (ng/h/mL)</strong></td>
<td>10,047 (8482–11,921)</td>
<td>4933 (3997–6089)</td>
<td>1.02 (0.83–1.25)</td>
</tr>
<tr>
<td><strong>Cmax (ng/mL)</strong></td>
<td>2504 (1996–3140)</td>
<td>1313 (1070–1610)</td>
<td>0.95 (0.75–1.20)</td>
</tr>
<tr>
<td><strong>tmax (h)</strong></td>
<td>0.41 (0.34–0.49)</td>
<td>0.44 (0.35–0.55)</td>
<td>0.94 (0.75–1.17)</td>
</tr>
<tr>
<td><strong>t1/2 (h)</strong></td>
<td>2.3 (2.0–2.6)</td>
<td>2.3 (2.0–2.7)</td>
<td>0.99 (0.85–1.14)</td>
</tr>
<tr>
<td>1 week postpartum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AUC (ng/h/mL)</strong></td>
<td>9896 (7832–12,505)</td>
<td>5082 (3749–6889)</td>
<td>0.97 (0.73–1.31)</td>
</tr>
<tr>
<td><strong>Cmax (ng/mL)</strong></td>
<td>2433 (1761–3363)</td>
<td>1210 (981–1492)</td>
<td>1.01 (0.75–1.35)</td>
</tr>
<tr>
<td><strong>tmax (h)</strong></td>
<td>1.0 (0.5–4.0)</td>
<td>1.5 (0.5–4.0)</td>
<td></td>
</tr>
<tr>
<td><strong>CL/F (L/h/kg)</strong></td>
<td>0.45 (0.35–0.58)</td>
<td>0.46 (0.32–0.66)</td>
<td>0.98 (0.70–1.37)</td>
</tr>
<tr>
<td><strong>t1/2 (h)</strong></td>
<td>5.9 (4.1–8.7)</td>
<td>6.6 (4.9–9.2)</td>
<td>0.90 (0.62–1.32)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are geometric least square mean (95% confidence interval); tmax, median (range); AUC = area under curve (to infinity for single dose, prepartum, and to dosing interval [t], postpartum); Cmax = observed peak concentration; tmax = time of peak concentration; CL/F = oral clearance; t1/2 = half-life.

* Geometric least-squares mean ratio (90% confidence interval).

* AUC and Cmax dose-normalized for comparisons.

* Half-life estimate underpredicted due to truncated sampling at 12 h (dosing interval).
Both cohorts showed broadly similar changes in virus load following therapy (Figure 4). Levels of HIV-1 RNA were virtually unchanged over the first 24 h of therapy regardless of assigned treatment group. During the first week of therapy, an average reduction of plasma HIV-1 levels $\approx$10-fold ($1 \log_{10}$) was observed in both the lamivudine monotherapy and combination groups. There was a large variation in the length of treatment before the onset of labor (median, 16 days; range, 0–28).

By the onset of labor, mean virus reduction was $>1.5$ logs in both groups, and this reduction was virtually unchanged at delivery. When the 3 women who were below the limit of quantitation before therapy were excluded, $\sim$25% and $\sim$75% of women had $<500$ HIV-1 RNA copies/mL at the start of labor and at delivery in the monotherapy and combination groups, respectively. It is important to note, however, that the lamivudine monotherapy group had higher baseline levels of HIV-1 and were treated an average of 2 days less before the start of labor.

In the lamivudine monotherapy arm, maternal virus load was $\leq 3 \log_{10}$ (1000 copies/mL) for all patients but 2 at delivery. One of the 2 began labor on the day that she was to begin therapy; the other showed a rebound in virus load. Patients assigned to the lamivudine plus zidovudine arm also had large reductions in HIV-1 load over the first days of therapy. At delivery, maternal virus load was $\leq 3 \log_{10}$ (1000 copies/mL) for all patients receiving combination therapy, and there was little sign of rebound in virus load in these patients. Further reductions in mean virus load at 1 and 2 weeks after delivery indicate that peak reductions in maternal virus load did not occur before delivery.

Two patients assigned to lamivudine monotherapy had evidence of virus rebound, 1 before and 1 after delivery. In both, the rebound was characterized by a predominance of virus with M184 Val substitution.

HIV-1 RNA could not be detected in the neonates at birth or 1 or 2 weeks after birth. At 12 months of follow-up, 15 babies were HIV antibody-negative and 1 was antibody positive by ELISA. Two died of nondrug- or HIV-1-related incidents, and 2 were lost to follow-up prior to the 9- and 12-month evaluations.

**Discussion**

Lamivudine alone and with zidovudine was well-tolerated in the women treated and in their neonates. No serious adverse events were considered related to the antiretroviral therapy in the mothers or infants. Laboratory results, including hemoglobin levels, in this small group of patients did not raise significant concerns. In particular, oral intrapartum therapy was well-tolerated and no nausea or vomiting were reported.

**Pharmacokinetics.** Lamivudine pharmacokinetic param-
eter estimates at week 38 of pregnancy, at 1 week after delivery, and in combination with zidovudine were similar to previous estimates in nonpregnant adults and demonstrate the lack of effect of pregnancy or combination therapy on lamivudine disposition. Consequently, no dose modification should be required. The concept of a loading dose at the onset of labor (given if the preceding dose was >6 h earlier) was introduced to ensure that all women, regardless of variability in pharmacokinetic disposition, achieved adequate serum concentrations intrapartum. Lamivudine was present (trough concentrations = 80 ng/mL) in all mothers through labor with our regimen. Results from the high-dose lamivudine monotherapy group (300 mg twice/day) showed that 300 mg was safe and well-tolerated in this patient group. There were no increases in incidence or severity of adverse events causally related to treatment. Consequently, a 150-mg lamivudine and a 300-mg zidovudine loading dose at the onset of labor should not present any clinical concern and should ensure adequate serum concentrations through this important period as previous compliance may be unknown.

Although sampling was limited, maternal zidovudine concentrations decayed in a biexponential manner. Maternal zidovudine pharmacokinetic parameters at week 38 of pregnancy were similar to those previously observed in adult males and in nonpregnant females. Zidovudine pharmacokinetic parameter estimates for AUC and CL/F differed between late pregnancy and 1 week postpartum; these results were similar to others in 3 patients studied before delivery and 3–4 weeks postpartum [12] and may be a consequence of physiologic changes following birth.

The 300-mg zidovudine regimen taken orally every 3 h with a loading dose at the onset of labor was based on theoretical considerations to obtain exposures comparable to those in the ACTG 076 intravenous regimen. Maternal, cord blood, and neonatal zidovudine concentrations at birth presented in this report and in a study in Thailand that used the same oral regimen were also similar to the intermittent infusion dosing schedule reported in ACTG 082 [13, 14]. The average predicted zidovudine concentration during labor with the oral intermittent regimen in this study was similar to that reported with a continuous infusion regimen (at the end of infusion), ~ 860 ± 180 and 1020 ± 900 ng/mL, respectively.

At birth, concentrations of lamivudine and zidovudine were similar in maternal, cord, and neonatal serum, illustrating free passage across the placenta. This is not unexpected given that both drugs are extensively distributed, have a relatively low molecular weight, and display limited plasma protein binding. In addition, ex vivo human placenta data support passive diffusion of lamivudine and zidovudine [15, 16].

Lamivudine was present in amniotic fluid and breast milk. Although the drug reaches breast milk, the actual concentration coupled with the average feed volume suggests the amount of drug a suckling neonate would ingest via this route is negligible relative to the standard oral dosing regimen and would not provide adequate antiretroviral drug concentrations for a neonate.

Decreased lamivudine oral clearance in the neonate is likely due to immature renal function at birth. Although glomerular

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**Figure 3.** Lamivudine and zidovudine (mean ± SD) deviation serum concentration vs. time in neonates after steady-state oral treatment. Lamivudine: 4 mg/kg 2 times/day (C), lamivudine 4 mg/kg 2 times/day + zidovudine (□), and zidovudine 2 mg/kg 4 times/day + lamivudine (△).

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**Table 2.** Neonatal steady-state pharmacokinetic parameters following oral administration of lamivudine (LAM) for 1 week.

<table>
<thead>
<tr>
<th></th>
<th>Monotherapy (4 mg/kg twice/day)</th>
<th>With AZT (2 mg/kg 4 times/day)</th>
<th>Comparison*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (ng/h/mL)</td>
<td>16,883 (13,395–21,278)</td>
<td>15,627 (12,367–19,746)</td>
<td>1.07 (0.85–1.33)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>1969 (1671–2323)</td>
<td>1689 (1268–2218)</td>
<td>1.17 (0.91–1.49)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>3.0 (1.0–8.0)</td>
<td>3.0 (1.0–3.0)</td>
<td>—</td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>1.11 (0.9–1.3)</td>
<td>1.2 (0.8–1.6)</td>
<td>0.90 (0.71–1.14)</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>6.0 (5.1–6.8)</td>
<td>6.6 (5.3–7.9)</td>
<td>0.90 (0.76–1.07)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are geometric least square mean (95% confidence interval); Cmax = observed peak concentration; CL/F = oral clearance, t1/2 = half-life, AZT = zidovudine.

* Geometric least-squares mean ratio (90% confidence interval).
Filtration develops rapidly, tubular secretion can often take 1–3 months to fully develop [17, 18]. Differences in absorption may also confound interpretation of oral clearance. The elimination half-life and exposure (as measured by AUC) are increased as a result of decreased lamivudine clearance relative to pediatric patients and reflect changes in renal function, especially development of active tubular secretion during early development. From a safety perspective, $C_{\text{max}}$ values in this study were within the range of those seen previously (1–2 mg/mL) as was overall exposure (20 mg/kg/day, 12,000/h/ng/mL) in children ages 3 months–2 years [19].

Zidovudine elimination in neonates at age 1 week was significantly increased compared to values immediately after birth. Absorption in neonates is variable because of irregular gastrointestinal function and irregular feeding.

Antiretroviral activity. Both lamivudine monotherapy and lamivudine plus zidovudine combination therapy produced rapid and substantial declines in maternal plasma HIV-1 RNA levels beginning 24 h after initiation of zidovudine therapy. Of importance, HIV-1 could not be detected by quantitative PCR in any neonate at birth or at 1 or 2 weeks after birth. This suggests either the complete absence of HIV-1 or extremely low levels of viral replication in these neonates.

Two patients received lamivudine monotherapy ≥25 days, and both showed an increase in virus load associated with the selection of virus with a mutation at HIV-1 RT codon 184V. Because it is not possible to predict precisely when labor will start, lamivudine monotherapy cannot be relied upon to maintain viral suppression even during short courses of therapy, as described here.

Lamivudine and lamivudine plus zidovudine were well-tolerated in women during late pregnancy and in their neonates in this study. The adverse event profile (laboratory safety data, adverse events) was similar to that expected in such a patient group.

Late pregnancy did not affect lamivudine or zidovudine pharmacokinetics, and no pharmacokinetic interaction between lamivudine and zidovudine was observed. Maternal zidovudine oral clearance at 1 week postpartum was decreased. Both drugs freely crossed the placenta and were secreted in breast milk. Oral zidovudine therapy during labor produced maternal, cord blood, and neonatal concentrations similar to intermittent intravenous and oral dosing regimens. Oral zidovudine intrapartum dosing (300 mg at onset of labor, then every 3 h until delivery) with lamivudine was predicted to provide average concentrations over a 3-h interval similar to those seen with the continuous intravenous infusion regimen ultimately used in ACTG 076.

A rapid reduction in virus load was seen in all mothers, although the use of lamivudine monotherapy would be anticipated to be associated with an increased risk of resistance. Very low or no HIV-1 was detected in neonates at birth. These data suggest that reduction in maternal virus load before delivery and a short course of therapy to neonates may give effective protection against HIV vertical transmission.

The recommended lamivudine pediatric dose (8 mg/kg/day) should be reduced in neonates to 4 mg/kg/day (divided as appropriate) to provide similar pediatric and adult daily exposure. This dosage should be increased to the pediatric recommended dosage (8 mg/kg/day) by 3 months of age, depending on renal

Figure 4. Maternal virus load in pregnant HIV-1–infected women treated with lamivudine or zidovudine plus lamivudine. Mean plasma HIV-1 levels (±SEM) determined by quantitative polymerase chain reaction are shown relative to initiation of lamivudine monotherapy (○) or zidovudine plus lamivudine (□). Nominal lower limit: 500 copies/mL (dashed line). No. of patients per arm was not constant due to variable times between start of therapy and birth.
function. Until further data are available for different zido-
vudine dose regimens for neonates, the recommended neo-
natal dose of 8 mg/kg/day (divided as appropriate) should be
maintained.

The combination of lamivudine plus zidovudine in short
practical oral regimens, such as used in this study, should be
investigated further in developing countries. The UNAIDS-
sponsored PETRA study in South Africa, Tanzania, and
Uganda is currently investigating the use of three regimens of
lamivudine plus zidovudine versus placebo with the aim of
identifying the most effective and applicable regimen with re-
spect to efficacy, tolerance, and cost.

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