Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Efavirenz (EFV, Sustiva) *(Last updated April 14, 2020; last reviewed April 14, 2020)*

**Formulations**

**Capsules:** 50 mg, 200 mg  
**Tablet:** 600 mg  

**Generic Formulations:**  
- 50 mg and 200 mg capsules  
- 600 mg tablet  

**Fixed-Dose Combination Tablets:**  
- [Atripla and generic] Efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg  
- [Symfi] Efavirenz 600 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg  
- [Symfi Lo] Efavirenz 400 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg  

When using fixed-dose combination (FDC) tablets, refer to other sections of the Drug Appendix for information about the individual components of the FDC. See also Appendix A, Table 2, Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.

For additional information, see Drugs@FDA or DailyMed.

**Dosing Recommendations**

**Neonatal Dose:**  
- Efavirenz (EFV) is not approved for use in neonates.

**Pediatric Dose:**  
- EFV capsules can be opened and the contents used as a sprinkle preparation for infants and children who are unable to swallow capsules.

**Infants and Children Aged 3 Months to <3 Years and Weighing ≥3.5 kg:**  
- The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) **does not recommend** the use of EFV in children aged 3 months to <3 years due to highly variable pharmacokinetics in this age group.

- If the use of EFV is unavoidable due to a clinical situation, the Panel suggests using investigational doses of EFV in this age group (see Table A in the Pharmacokinetics and Dosing: Infants and Children Aged <3 Years section below). Evaluation of cytochrome P450 (CYP) 2B6 genotype is required prior to use of EFV in this age group. Therapeutic drug monitoring (TDM) should be used and EFV plasma concentration should be measured 2 weeks after initiation. If a child initiated

**Selected Adverse Events**

- Rash, which is generally mild and transient and appears to be more common in children than in adults  
- Central nervous system (CNS) symptoms, such as fatigue, poor sleeping patterns, insomnia, vivid dreams, impaired concentration, agitation, seizures, depression, suicidal ideation, **late-onset ataxia, and encephalopathy**  
- Use of EFV may produce false-positive results with some cannabinoid and benzodiazepine tests.  
- Gynecomastia  
- Hepatotoxicity  
- Corrected QT prolongation

**Special Instructions**

- EFV capsules and tablets can be swallowed whole, or EFV capsules can be administered by sprinkling the contents of an opened capsule on food as described below.  
- Bedtime dosing is recommended, particularly during the first 2 to 4 weeks of therapy, to improve tolerability of CNS side effects.  
- Administer EFV, Atripla, Symfi, or Symfi Lo on an empty stomach. Avoid administration with
EFV at an investigational dose while aged <3 years, some experts would also measure EFV plasma concentration at age 3 years after the child transitions to the recommended dose for children aged ≥3 years (see the Therapeutic Drug Monitoring section below). When making a dose adjustment based on EFV concentrations, consultation with an expert in pediatric HIV infection is recommended.

Children Aged ≥3 Years and Weighing ≥10 kg:

### Once-Daily Doses of Efavirenz by Weight

<table>
<thead>
<tr>
<th>Weight</th>
<th>EFV Dosea,b</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 kg to &lt;15 kg</td>
<td>200 mg</td>
</tr>
<tr>
<td>15 kg to &lt;20 kg</td>
<td>250 mg</td>
</tr>
<tr>
<td>20 kg to &lt;25 kg</td>
<td>300 mg</td>
</tr>
<tr>
<td>25 kg to &lt;32.5 kg</td>
<td>350 mg</td>
</tr>
<tr>
<td>32.5 kg to &lt;40 kg</td>
<td>400 mg</td>
</tr>
<tr>
<td>≥40 kg</td>
<td>600 mg</td>
</tr>
</tbody>
</table>

a The dose in mg can be dispensed in any combination of capsule strengths. Capsules may be administered by sprinkling the contents onto an age-appropriate food (see Special Instructions).

b Some experts recommend a dose of EFV 367 mg per m² of body surface area (maximum dose 600 mg) due to concerns about underdosing at the upper end of each weight band (see the Pediatric Use section below for details). Weight bands approximate a dose of EFV 367 mg per m² of body surface area, with a maximum dose of 600 mg.

Child and Adolescent (Weighing ≥40 kg) and Adult Dose:
- EFV 600 mg once daily

[**Atripla**] Efavirenz 600 mg/Emtricitabine/Tenofovir Disoproxil Fumarate (TDF)

Child and Adolescent (Weighing ≥40 kg) and Adult Dose:
- One tablet once daily
- Take on an empty stomach.

[**Symfi**] Efavirenz 600 mg/Lamivudine/TDF

Child and Adolescent (Weighing ≥40 kg) and Adult Dose:
- One tablet once daily
- Take on an empty stomach.

[**Symfi Lo**] Efavirenz 400 mg/Lamivudine/TDF

Child and Adolescent (Weighing ≥35 kg) and Adult Dose:
- One tablet once daily
- Take on an empty stomach.

### Instructions for Using the Efavirenz Capsule as a Sprinkle Preparation with Food or Formula:
- Hold capsule horizontally over a small container and carefully twist open to avoid spillage.
- Gently mix capsule contents with 1 to 2 teaspoons of an age-appropriate soft food (e.g., applesauce, grape jelly, yogurt) or reconstituted infant formula at room temperature.
- Administer within 30 minutes of mixing and do not consume additional food or formula for 2 hours after administration.

### Metabolism/Elimination
- CYP2B6 is the primary enzyme for EFV metabolism.
- CYP3A and CYP2B6 inducer in vivo
- EFV is not recommended for patients with moderate or severe hepatic impairment.
- Interpatient variability in EFV exposure can be explained in part by polymorphisms in CYP450, particularly CYP2B6 polymorphisms. Slower metabolizers are at higher risk of toxicity (see the Therapeutic Drug Monitoring section below for information about the management of mild or moderate toxicity).

### Atripla, Symfi, and Symfi Lo Dosing in Adults with Renal Impairment:
- Because these are FDC products, and because TDF, lamivudine, and emtricitabine require dose adjustments based on renal function, Atripla, Symfi, and Symfi Lo should not be used in patients with creatinine clearance <50 mL/min or in patients on dialysis.
Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and HIV Drug Interaction Checker)

- **Metabolism:** Coadministration of efavirenz (EFV) with drugs that are primarily metabolized by cytochrome P450 (CYP) 2C9, CYP2C19, CYP2B6, or CYP3A isozymes may result in altered plasma concentrations of the coadministered drugs. Drugs that induce CYP3A and CYP2B6 activity would be expected to increase the clearance of EFV, resulting in lower plasma concentrations. There is potential for multiple drug interactions with EFV. Importantly, dose adjustment or the addition of ritonavir may be necessary when EFV is used in combination with atazanavir (ATV), lopinavir/ritonavir (LPV/r), or maraviroc (MVC).

- Before EFV is administered, a patient’s medication profile should be carefully reviewed for potential drug interactions with EFV.

- Corrected QT (QTc) prolongation has been observed with the use of EFV.\(^1,2\) Consider using an alternative to EFV in patients who are receiving a drug that has a known risk of Torsades de Pointes or in patients who are at higher risk of Torsades de Pointes.

Major Toxicities

- **More common:** Skin rash, increased transaminase levels. Central nervous system (CNS) abnormalities such as dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, euphoria, and seizures have been reported, primarily in adults (see Table 15a for information on managing these toxicities).

- **Rare:** QTc prolongation has been observed with the use of EFV.\(^1,2\) A case report associated EFV use with marked QT prolongation and Torsades de Pointes.\(^3\) An association between EFV and suicidal ideation, suicide, and attempted suicide (especially among those with a history of mental illness or substance abuse) was found in one retrospective analysis of four comparative trials in adults. This association, however, was not found in analyses of two large observational cohorts.

- **Potential risk of teratogenicity:** See Efavirenz in the Perinatal Guidelines.

Resistance

The International Antiviral Society-USA (IAS-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

EFV has been approved by the Food and Drug Administration (FDA) for use as part of antiretroviral (ARV) therapy in children aged ≥3 months and weighing ≥3.5 kg. The FDA has also approved the use of Symfi Lo, Note: Symfi Lo has not been studied in children (sexual maturity ratings [SMRs] 1–3), and major interindividual variability in EFV plasma concentrations has been found in pediatric patients in a multiethnic setting. The 400 mg dose of EFV may be too low in children or adolescents with SMRs 1 to 3 who weigh ≥40 kg. The use of TDM is suggested by some Panel members when Symfi Lo is used in pediatric patients who weigh ≥40 kg (see the Therapeutic Drug Monitoring section below).
the fixed-dose combination of EFV 400 mg/lamivudine (3TC) 300 mg/tenofovir disoproxil fumarate (TDF) 300 mg, in children weighing ≥35 kg.

**Efficacy in Clinical Trials**

EFV-based regimens have proven virologically superior or noninferior to a variety of regimens in adults, including those containing LPV/r, nevirapine, rilpivirine, ATV, elvitegravir, raltegravir, and MVC.4-10 EFV was shown to be inferior to dolutegravir (DTG) in the SINGLE trial in adults, which compared the virologic response of DTG plus abacavir/3TC to the virologic response of EFV/TDF/emtricitabine (FTC) at Weeks 48 and 144. The differences were most likely due to more drug discontinuations in the EFV group.11

In clinical trials in adults and children with HIV, EFV used in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) has been associated with excellent virologic response. FDA approval of Symfi (EFV 600 mg/3TC/TDF) was based on the results from a clinical trial that compared the use of TDF to the use of stavudine when each drug was administered with 3TC and EFV.12 This trial showed that these regimens were similarly effective. The 96-week results of the Encore1 trial, a randomized trial in adults, showed that EFV 400 mg used in combination with TDF and FTC was noninferior to EFV 600 mg used in combination with TDF and FTC.13 EFV used in combination with two NRTIs or with an NRTI and a protease inhibitor has been studied in children and has shown virologic potency and safety that is comparable to what has been seen in adults.14-20

FDA approval of Symfi Lo (EFV 400 mg/3TC/TDF) was based on a comparison between EFV 400 mg and EFV 600 mg, both taken with FTC 200 mg plus TDF 300 mg in 630 ARV-naive adult participants with a mean age of 36 years (range 18–69 years). Sixty-eight percent of participants were male, 37% were of African heritage, 33% were of Asian ethnicity, 17% were Hispanic, and 13% were Caucasian. This study showed similar rates of viral load suppression and toxicities among participants in each group.13 Since EFV clearance is related to age and to CYP2B6 polymorphisms, and since allele frequency varies by ethnicity, some members of the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) suggest using therapeutic drug monitoring (TDM) when using Symfi Lo in pediatric patients weighing ≥40 kg.

**Pharmacokinetics: Pharmacogenomics**

Genetic polymorphisms in the genes that code for enzymes involved in the metabolism of EFV may alter enzyme activity, which causes a high degree of interpatient variability in drug exposure. CYP2B6 is the primary enzyme for EFV metabolism, and pediatric patients with the CYP2B6-516-T/T genotype have reduced metabolism, resulting in higher EFV levels in these patients than in those with the G/G or G/T genotypes.21-25 The CYP2B6-516-T/T allele frequency varies by ethnicity. In a study of adults from the United States and Italy, this allele had a frequency of 24.4% among white study participants, a frequency of 31.3% among black study participants, and a frequency of 34.9% among Hispanic study participants.26 A retrospective study of pediatric patients in a multi-ethnic, high-income setting confirmed that EFV plasma concentrations can vary between patients. The interindividual variability could be explained in large part by polymorphisms in drug metabolizing genes, as well as by age at treatment initiation and time since treatment initiation.27 IMPAACT P1070 has shown that aggressive dosing with approximately 40 mg/kg of EFV using opened capsules resulted in therapeutic EFV concentrations in 58% of children aged <3 years with the G/G or G/T genotypes, but excessive exposure occurred in those with the T/T genotype.28 Optimal dosing may require pretreatment CYP2B6 genotyping in children aged <3 years (see discussion below).25,28

Other variant CYP2B6 alleles and variant CYP2A6 alleles have been found to influence EFV concentrations in adults and children.25,29-33 The CYP2B6 T983C mutation has also been associated with reduced EFV clearance in African children.25

**Pharmacokinetics and Dosing: Infants and Children Aged <3 Years**

The Panel does not recommend the use of EFV in children aged 3 months to <3 years. Limited pharmacokinetic (PK) data in children aged <3 years or weighing <13 kg have shown that it is difficult
to achieve target trough concentrations in this age group.\textsuperscript{23,34} These data show age-related differences in absorption and the impact of formulation on EFV PKs.\textsuperscript{24} Also, hepatic enzyme activity is known to change with age. Using a pharmacometric model, the increase in oral clearance of EFV as a function of age is predicted to reach 90\% of mature value by age 9 months.\textsuperscript{24} This maturation of oral clearance is postulated to result from an increase in the expression of CYP2B6 with age.\textsuperscript{24} The CYP2B6-516-G/G genotype is associated with the greatest expression of hepatic CYP2B6 when compared with the CYP2B6-516-G/T or -T/T genotypes.\textsuperscript{21} In children with the CYP2B6-516-G/G genotype, the oral clearance rate of EFV has been shown to be higher in children aged <5 years than in older children.\textsuperscript{21} Efficacy data for opened capsules with contents used as a sprinkle preparation suggest acceptable palatability and bioavailability for infants and children aged <3 years; however, the difficulty associated with sprinkling the contents of opened capsules contributes to the variability of PK measures in this age group.

IMPAACT P1070 studied children aged <3 years with HIV and tuberculosis (TB) coinfection, using doses of EFV that were determined by weight band based on CYP2B6-516-G/G and -G/T genotypes: children with G/G and G/T genotypes were considered extensive metabolizers (EMs) and children with T/T genotypes were considered slow metabolizers (SMs) (see Table A below). When doses were used without regard to genotype, a dose of approximately 40 mg/kg per day resulted in therapeutic EFV concentrations in an increased proportion of study participants with G/G or G/T genotypes but excessive exposure in a high proportion of participants with T/T genotypes. This dose is higher than the FDA-approved dose of EFV.\textsuperscript{28} Therefore, doses were modified so that infants and young children with the T/T genotype received a reduced dose. The doses listed for P1070 in Table A are investigational.

A recent study evaluated the PKs of EFV in children aged <3 years who had TB/HIV coinfection and who were receiving anti-TB treatment with rifampicin, isoniazid, pyrazinamide, and ethambutol. The findings from this study reinforced the use of CYP2B6-516 genotype-directed EFV dosing and showed that, in general, the EFV weight-band dose did not need to be modified further for children aged <24 months. Dosing for children aged 24 to 36 months requires further investigation.\textsuperscript{35}

**Investigational Dosing for Children Aged 3 Months to <3 Years By CYP2B6 Genotype**

**Table A. Comparison of Efavirenz Doses Used in P1070 and the FDA-Recommended Doses**

<table>
<thead>
<tr>
<th>Weight</th>
<th>Protocol P1070 Dosing for Patients with CYP2B6-516-G/G and -G/T Genotypes (EMs)\textsuperscript{a}</th>
<th>Protocol P1070 Dosing for Patients with CYP2B6-516-T/T Genotype (SMs)\textsuperscript{a}</th>
<th>FDA-Approved Dosing for Children Aged 3 Months to &lt;3 Years (Without Regard to CYP2B6 Genotype)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 kg to &lt;7 kg</td>
<td>300 mg</td>
<td>50 mg</td>
<td>150 mg</td>
</tr>
<tr>
<td>7 kg to 7.5 kg</td>
<td>400 mg</td>
<td>100 mg</td>
<td>150 mg</td>
</tr>
<tr>
<td>7.5 kg to &lt;10 kg</td>
<td>400 mg</td>
<td>100 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td>10 kg to &lt;14 kg</td>
<td>400 mg</td>
<td>100 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td>14 kg to &lt;15 kg</td>
<td>500 mg</td>
<td>150 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td>15 kg to ≤17 kg</td>
<td>500 mg</td>
<td>150 mg</td>
<td>250 mg</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Investigational doses are based on IMPAACT study P1070.\textsuperscript{28,35} Evaluation of CYP2B6 genotype is required before initiating EFV. Therapeutic drug level monitoring is recommended, with a trough concentration measured 2 weeks after initiating EFV and again at age 3 years for a possible dose adjustment.

**Key:** CYP = cytochrome P450; EFV = efavirenz; EM = extensive metabolizer; FDA = Food and Drug Administration; SM = slow metabolizer

The FDA-approved doses of EFV for use in infants and children aged 3 months to <3 years were derived from a population PK model that was based on data from older subjects in PACTG 1021 and PACTG 382, and also from data collected during AI266-922, a study that assessed the PKs, safety, and efficacy of using capsule sprinkles in children aged 3 months to 6 years (see Table A). The FDA-approved doses are lower
than the CYP2B6 EM doses and higher than the CYP2B6 SM doses from the P1070 study. PK modeling, based on P1070 PK data, was used to generate estimates of the percentage of participants who were likely to reach therapeutic EFV target concentrations on FDA-indicated doses, according to the participants’ genotypes.\(^{28}\) The study reported that an estimated one-third of EM children who received the FDA-approved dose would experience subtherapeutic EFV exposures, and more than half of SM children who received the FDA-approved dose would have area under the curve (AUC) values that were above the target range.

The Panel \textbf{does not recommend} use of EFV in children aged 3 months to \(<3\) years. If the clinical situation demands the use of EFV, the Panel recommends determining CYP2B6 genotype prior to use (see a \textit{list of laboratories that perform this test}). Patients should be classified as extensive CYP2B6-516-G/G and -G/T genotype metabolizers or slow CYP2B6-516-T/T genotype metabolizers to guide dosing as indicated by the investigational doses from IMPAACT study P1070 (see Table A). Whether the doses used are investigational or approved by the FDA, EFV plasma concentrations should be measured 2 weeks after initiating EFV (see the Therapeutic Drug Monitoring section below). The mid-dose EFV plasma concentration target of 1.0 mg/L to 4.0 mg/L derived from adult clinical monitoring data is typically also applied to trough concentrations. A study of 128 African children (aged 1.7–13.5 years) suggests that the C\(_{24h}\) threshold for increased risk of unsuppressed viral load is C\(_{24h}\) 0.65 mg/L.\(^{36}\) Consultation with an expert in pediatric HIV infection is recommended before adjusting dose. In addition, when following the P1070 investigational dose recommendations, some experts would measure EFV concentrations at age 3 years before transitioning the child to the recommended dose for children aged \(\geq 3\) years.

**Pharmacokinetics: Children Aged \(\geq 3\) Years and Adolescents**

Even with the use of FDA-approved pediatric dosing in children aged \(\geq 3\) years, EFV concentrations can be suboptimal.\(^{21,37-41}\) Therefore, some experts recommend using TDM in patients who are receiving EFV and possibly using higher doses in young children, especially in certain clinical situations, such as virologic rebound or lack of response in an adherent patient. In one study in which the EFV dose was adjusted in response to measurement of the AUC, the median administered dose was EFV 13 mg/kg (367 mg per m\(^2\) of body surface area) and the range was from 3 mg/kg to 23 mg/kg (69–559 mg per m\(^2\) of body surface area).\(^{42}\)

**Toxicity: Children versus Adults**

The toxicity profile for EFV differs for adults and children. One adverse effect (AE) commonly seen in children is rash, which was reported in up to 40% of children and 27% of adults.\(^{43}\) The rash is usually maculopapular, pruritic, mild to moderate in severity, and rarely requires drug discontinuation. Onset is typically during the first 2 weeks of treatment. Although severe rash and Stevens-Johnson syndrome have been reported, they are rare.

In adults, CNS symptoms are commonly reported, affecting 29.6% of patients in one meta-analysis of randomized trials.\(^{44}\) These symptoms usually occur early in treatment and rarely require drug discontinuation, but they can sometimes persist for months. Administering EFV at bedtime appears to decrease the occurrence and severity of these neuropsychiatric AEs. For patients who can swallow capsules or tablets, ensuring that EFV is taken on an empty stomach also reduces the occurrence of neuropsychiatric AEs. In several studies, the incidence of neuropsychiatric AEs was correlated with EFV plasma concentrations, and the symptoms occurred more frequently in patients with higher concentrations.\(^{45-48}\) The ENCORE1 study in adults demonstrated that a dose of EFV 400 mg is associated with fewer AEs and a noninferior virologic response when compared with the recommended 600-mg dose of EFV.\(^{13,49}\) A Tanzanian study of children aged 6 to 12 years showed that those who were receiving EFV, especially doses of EFV that were higher than or equal to those recommended by the World Health Organization, had more anxiety and more difficulty concentrating at school than children who were receiving alternative ARV medications.\(^{50}\) Adverse CNS events occurred in 14% of children who received EFV in clinical studies\(^{51}\) and in 30% of children with plasma EFV concentrations >4 mg/L.\(^{22}\) Late-onset neurotoxicity, including ataxia and encephalopathy, may occur months to years after initiating EFV. Some events of late-onset neurotoxicity have occurred in patients with certain CYP2B6 genetic polymorphisms who received standard doses of EFV. These polymorphisms have been
associated with slow metabolism of EFV and increased EFV levels (see the package insert for EFV).

An association between EFV and suicidal ideation, suicide, and attempted suicide (especially among those with a history of mental illness or substance abuse) was found in a retrospective analysis of four comparative trials in adults and in the START Trial, a prospective analysis of adults. This association, however, was not found in analyses of two large observational cohorts, and no cases of suicide were reported in a systematic review of randomized trials. In patients with pre-existing psychiatric conditions, EFV should be used cautiously.

Toxicity: QTc Prolongation

The effect of EFV on the QTc interval was evaluated in a study of 58 healthy adult participants; a variety of CYP2B6 polymorphisms was represented within this group. A positive relationship between EFV concentration and QTc prolongation was observed. Consider using an alternative to EFV in patients who are receiving a drug that has a known risk of Torsades de Pointes (e.g., quinidine, clarithromycin) or in patients who are at higher risk of Torsades de Pointes.

Therapeutic Drug Monitoring

It is reasonable for a clinician to use TDM to determine whether a patient is experiencing toxicity because the concentration of EFV is higher than the normal therapeutic range. Dose reduction or drug discontinuation would be considered appropriate management of drug toxicity. Dose reduction is best performed in consultation with an expert in pediatric HIV. Also, TDM should be considered when administering EFV to children aged 3 months to <3 years due to increased oral clearance and variable PK properties in this young age group. TDM should also be considered when using a lower dose of EFV, such as the dose found in Symfi Lo, in children weighing ≥40 kg. Two weeks after initiating EFV in patients aged <3 years, clinicians should measure the plasma concentration of EFV. In cases where a dose adjustment may be necessary, clinicians should consult an expert in pediatric HIV infection prior to adjusting the dose. If a child initiated EFV at an investigational dose while <3 years of age, some experts would also measure plasma concentration at age 3 years after the child transitions to the recommended dose for children aged ≥3 years.

The currently accepted minimum effective concentration of EFV is a mid-dose concentration (C_{12h}) >1 mg/L in adults, and concentrations of >4.0 mg/L are associated with CNS side effects. However, the validity using a single target has been called into question. In addition, a lower limit of C_{12h} >0.7mg/L was most predictive of virologic outcome in a study of 180 adults. Findings from a study of 128 African children (aged 1.7–13.5 years) suggest that the C_{24h} threshold for increased risk of unsuppressed viral load is C_{24h} 0.65 mg/L.

References


