Safety and Efficacy of Lopinavir/ritonavir (LPV/r)-based Antiretroviral Therapy in Pregnant Women: A Systematic Review

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Background

- Highly active antiretroviral therapy (HAART) has increased the lifespan of patients with HIV/AIDS
- Mother-to-child transmission (MTCT) rates are 15-45% without intervention. With intervention, MTCT rates can be decreased to <5%[1].
  - Due to these advances, more women with HIV/AIDS may consider pregnancy
- LPV/r is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. There are no adequate and well-controlled studies in pregnant women[2].
- The 2012 DHHS Perinatal Guidelines recommend the use of LPV/r + 2 nucleos(t)ide reverse transcriptase inhibitors (NRTIs) as a HAART intervention for the treatment of HIV-1 in pregnant women and to reduce the risk of MTCT[3]

1. Mother-to-child transmission of HIV. World Health Organization. http://www.who.int/hiv/topics/mtct/en/. 2. Kaletra (LPV/r) [package insert]. 2012. 3. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. http://aidsinfo.nih.gov/contentfiles/lvguidelines/perinatalgl.pdf.

Background

- Pharmacokinetic studies suggest that pregnant women receiving the standard dose of LPV/r (400/100 mg BID) experience declines in LPV/r plasma concentration during the 3rd trimester[1,2,3,4]

- Despite this decline in LPV/r plasma concentration, virologic response and MTCT rates appear to be adequate; however, these pharmacokinetic studies are not designed to assess clinical outcomes[1,5,6,7]

- **Objective: To assess maternal and infant clinical outcomes in a systematic review of published data on HIV-infected pregnant women treated with LPV/r-based regimens**

1. AIDS. 2006;20(15)1931-1939. 2. Curr Opin HIV AIDS. 2008;3(3):277-282. 3. J Acquir Immune Defic Syndr. 2008;54(4)381-388. 4. J Acquir Immune Defic Syndr. 2008;49(5):485-491. 5. HIV Clin Trials. 2007;8(4):254-255. 6. HIV Med. 2011;12(3):166-173. 7. AIDS. 2011;25(10)1299-1303.

Systematic Review Assessing Clinical Outcomes in HIV-1-infected Pregnant Women Treated with LPV/r

Inclusion Criteria:

- Publications/presentations describing prospective clinical studies or retrospective analyses reporting clinical outcomes in HIV-1-infected pregnant women and their infants
- Study participants were women receiving a LPV/r-based regimen (regardless of dose) during pregnancy

Exclusion Criteria:

- Review articles, letters to the editor, case studies, and primary pharmacokinetic studies
- Studies not including LPV/r use and HIV-infected pregnant women
- Studies without information on maternal or birth outcomes

Systematic Review Assessing Clinical Outcomes in HIV-1-infected Pregnant Women Treated with LPV/r

Search Strategy:

- Publications and presentations found through a search of PubMed, EMBASE, and abstracts from HIV Congresses
- Publications and presentations published from January 1995 to May 31, 2012

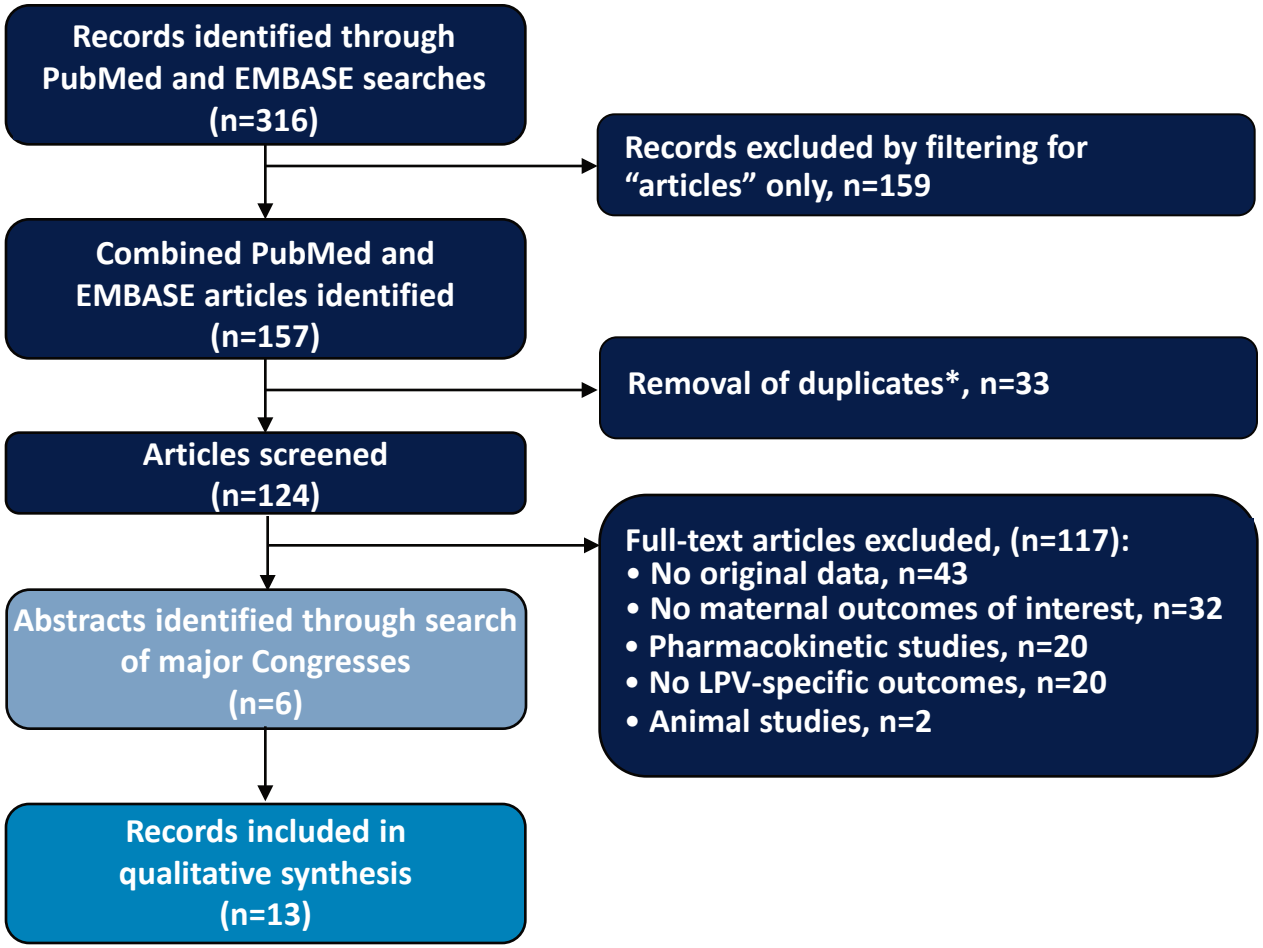
Review Process:

- Titles and abstracts were independently evaluated by 2 reviewers for inclusion, and differences were adjudicated by a third reviewer

Data Extraction:

- Data were extracted and tabulated from publications and presentations that met the inclusion criteria

Publications That Met Systematic Review Criteria



Thirteen publications/presentations describing 9 studies

*Articles found through searches of both databases

Systematic Review Evaluations

Baseline Demographics	• Baseline demographics and disease characteristics of pregnant women
Efficacy in Mothers	• Plasma HIV-1 RNA levels • $CD4^+$ T-cell counts
Pregnancy/Infant Outcomes	• Preterm delivery • Low birth weight • Stillbirths/live births • MTCT • Infant mortalities
Safety Outcomes in Mothers	• Mortalities and discontinuations • Serious adverse events (SAEs) • Grade 3 or 4 laboratory abnormalities

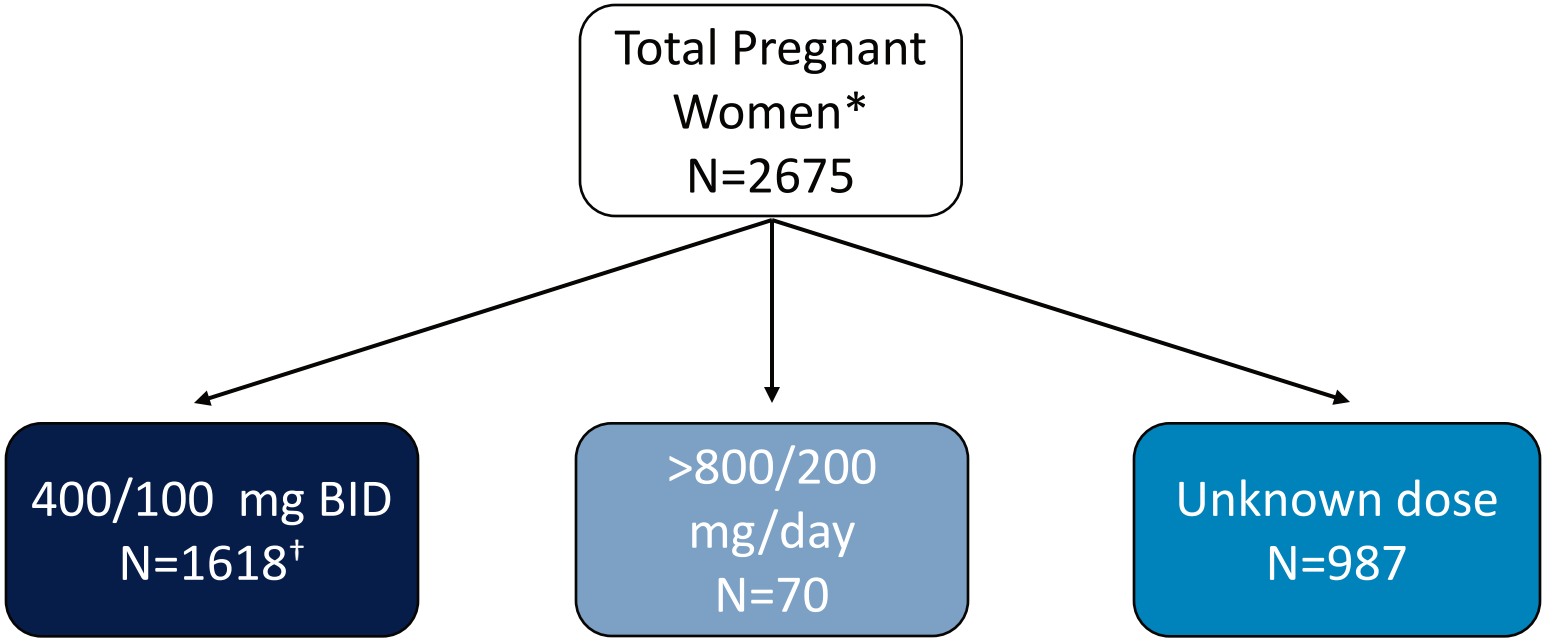
Characteristics of Included Studies

Study, Location	Number	Comparator	Study Design and Objectives*
Azria et al, France	100	Matched HIV-negative, pregnant women	Prospective- Maternal/neonatal safety of LPV/r; effect on pregnancy outcomes
Kesho Bora†, Kenya, South Africa	412	Zidovudine and sdNVP	Prospective, randomized- Efficacy and safety of different treatment regimens for MTCT prevention
Mma Bana†, Shapiro et al, Botswana	275	Abacavir/zidovudine/ lamivudine	Prospective, randomized- Virologic suppression, pregnancy outcomes, and safety in mothers and infants in response to different HAART regimens
Peixoto et al, Brazil			
• 800/200 mg/day	164	None	Prospective, non-randomized- Laboratory AEs according to standard and increased LPV/r dosing during 3rd trimester
• >800/200 mg/day	70		
Senise et al, Brazil	64	None	Retrospective- LPV/r impact, as part of HAART, on pregnancy outcomes and MTCT
PRIMEVA, Tubiana et al, France			
• LPV/r monotherapy	69	None	Prospective, randomized- control of HIV-1 RNA, and maternal/infant toxicities of LPV/r
• LPV/r HAART	36		
Mejia-Villatoro et al, Guatemala	219	None	Retrospective- MTCT outcomes following LPV/r treatment
Raha et al, Zambia	279	HAART-naïve, historical controls	Prospective, open-label, interventional- Safety and efficacy of extended duration HAART in pregnant and breastfeeding women
Roberts et al, Antiretroviral Pregnancy Registry	987	None	Prospective, cohort- Birth outcomes after pregnancy exposures to LPV/r

*LPV/r dose was 400/100 mg BID in all studies except for the Peixoto study, in which standard dose was 800/200 mg/day and increased dose was >800/200 mg/day, and the Roberts study, in which dose was not reported

†More than 1 included publication/presentation described the study

Subjects That Met Systematic Review Criteria



*Mean/median age of women enrolled ranged from 25-32.5 years

†1454 subjects received 400/100 mg BID;164 subjects received 800/200 mg/day with dosing interval not specified

Maternal Outcomes of HIV-1-infected Pregnant Women Treated With a LPV/r-based Regimen

Study	HIV-1 RNA at Entry (Copies/mL)	HIV-1 RNA Cut-off for Viral Suppression (Copies/mL)	Proportion of Women Achieving Viral Suppression at or Near Delivery
Azria	3981 (median)	≤200	88%
Kesho Bora	16 982 (median)	<300	64%
Mma Bana	9100 (median)	<400	93%
Peixoto			
• 800/200 mg/day	72%: <1000	<1000	88%
• >800/200 mg/day	76%: <1000		84%
Senise	31 100 (median)	<400	81%
PRIMEVA			
• LPV/r monotherapy	2952 (median)	<200	91%
• LPV/r HAART	2928 (median)		97%
Mejia-Villatoro	66 426 (median)	NR	NR
Raha	NR	NR	NR
Roberts	NR	NR	NR

NR=not reported

- **>80% achieved viral suppression as per the study cut-off (64% in Kesho Bora study)**
- **No difference in proportion of women with HIV-1 RNA levels ≥1000 copies/mL between the 800/200 mg/day and >800/200 mg/day groups in the Peixoto study (*P*=0.51)**

Maternal Outcomes of HIV-1-infected Pregnant Women Treated With a LPV/r-based Regimen

Study	$CD4^+$ T-Cell Count at Entry (cells/ml)	$CD4^+$ T-Cell Count at or Near Delivery (cells/ml)
Azria	361 (median)	434 (median)
Kesho Bora	336 (median)	463 (median)
Mma Bana	403 (median)	NR
Peixoto		
• 800/200 mg/day	486 (mean)	560 (mean)
• >800/200 mg/day	535 (mean)	606 (mean)
Senise	287 (median)	345 (median)
PRIMEVA • LPV/r monotherapy • LPV/r HAART	525 (median)	NR
Mejia-Villatoro	329 (mean)	NR
Raha	NR	NR
Roberts	NR	NR

NR=not reported

- **Maternal $CD4^+$ T-cell counts were increased at time of delivery in all 4 studies that reported $CD4^+$ T-cell counts at entry and at or near delivery**

Pregnancy Outcomes for Women Infected With HIV-1 and Treated With a LPV/r-based Regimen

Study	Preterm Delivery (<37 Weeks) n/N (%)	Very Preterm Delivery (<32 Weeks) n/N (%)	Low Birth Weight (<2500 g) n/N (%)	Very Low Birth Weight (<1500 g) n/N (%)	Stillbirths/ Live Births
Azria	16/100 (16.0)	5/100 (5.0)	17/100* (17.0)	3/100† (3.0)	NA
Kesho Bora	53/401 (13.2)	2/401 (0.5)	44/384 (11.5)	1/384 (0.3)	4/401
Mma Bana	61/270 (22.6)‡	1/270 (0.4)	45/270 (16.7)	1/270 (0.4)	5/270
Peixoto					
• 800/200 mg/day	16/163 (9.8)	NR	33/163 (20.2)	NR	NA
• >800/200 mg/day	6/69 (8.7)		11/69 (15.9)		
Senise	16/64 (25.0)	0§	13/64 (20.3)	0	NA
PRIMEVA					
• LPV/r monotherapy	NR	NR	NR	NR	NA
• LPV/r HAART					
Mejia-Villatoro	23/219 (10.6)	NR	NR	NR	10/200
Raha	NR	NR	42/229 (18.3)¶	2/229 (0.9)	8/230
Roberts	119/890 (13.4)	19/890 (2.1)	165/858 (19.2)	19/858 (2.2)	9/920

NA=not applicable, study inclusion criteria required mother-infant pair; NR= not reported
*,†Less than tenth or third percentile respectively according to the Leroy and Lefort curves
‡More common in LPV/r group vs. comparator (95% CI= <1 to 16)
§Very preterm delivery was defined as <30 weeks
¶Significantly different from comparator (*P*=0.005)

- **The rate of preterm delivery ranged from 8.7-25.0%**
- **The rate of low birth weight ranged from 11.5-20.3%**
- **The rate of stillbirths ranged from 1.0-4.8%**

Infant Outcomes

Study	MTCT* n/N (%)	Infant Mortality† n/N (%)
Azria	1/100 (1.0)	0/100 (0)
Kesho Bora	7/394 (1.8)	24/412 (5.8)
Mma Bana	1/270 (0.4)	7/270 (2.6)
Peixoto • 800/200 mg/day • >800/200 mg/day	 1/162 (0.6) 0/69 (0)	 NR
Senise	0/64 (0)	NR
PRIMEVA • LPV/r monotherapy • LPV/r HAART	 0/69 (0) 1/36 (2.8)	 NR
Mejia-Villatoro	3/219 (1.4)	NR
Raha	3/183 (1.6)	12/208 (5.8)
Roberts	NR	NR

NR= not reported
NA=not applicable, study inclusion criteria required mother-infant pair;
*Time of MTCT evaluation ranged from birth to 24 months
†Time of infant mortality evaluation ranged from 28 days to 12 months

- **Systematic review included 2021 live births**
- **MTCT rate ranged from 0-2.8%**

Maternal Safety

Mortality* (2 studies reporting, n=687): 0-1.0%[†,‡]

- No deaths attributed to LPV/r

Discontinuations (2 studies reporting, n=697): 0.4-1.7%[†,‡]

- No reasons for withdrawal stated

Maternal SAEs including obstetrical and post-partum complications (4 studies reporting, n=1011): 0-36.1% of subjects[†,‡,§,‖]

- Most common SAE by study (2 studies, n=687):
  - Infectious diseases: 34/412 (8.3%)[†]
  - Obstetric pathologies: 8/275 (2.9%)[‡]

Grade 3/4 Laboratory Events (3 studies reporting, n=914): 1.4-11.6% of subjects[†,‡,¶]

- Most common events by study:
  - Decreased hemoglobin: 10/377 (2.7%)[†]
  - Anemia: 12/275 (4.4%)[‡]
  - Increased cholesterol: 5/162 (3.1%)[¶, **]
  - Increased bilirubin: 1/68 (1.5%)[¶, ††]

*Mortality assessed within 12 months post-delivery in Kesho Bora study and within 6 months post delivery in Mma Bana study
[†]Kesho Bora, [‡]Mma Bana, [§]PRIMEVA (monotherapy and HAART arms assessed separately), [‖]Mejia-Villatoro,
[¶]Peixoto (**800/200 mg/day and [††]>800/200 mg/day arms assessed separately)

Limitations

- Only English language articles were included
- The majority of the selected publications described studies that used the standard LPV/r dose (400/100 mg BID)
- Rate of preterm delivery and low birth weight must be compared to the regional rates and cannot be generalized to other areas of the world
- Viral thresholds for response and timing of sample collection varied between studies
- Method for estimating gestational age varied by study
- Some studies included limited data sets, particularly for AEs

Conclusions

- This review included data from 2675 HIV-1-infected pregnant women treated with LPV/r and 2021 live births
- Although thresholds for viral response varied, there was a maternal pattern of adequate response to LPV/r therapy during pregnancy, consistent to that reported in non-pregnant subjects
  - Pregnant women receiving LPV/r therapy also demonstrated increases in $CD4^+$ T-cell counts at delivery
  - Safety, efficacy, and MTCT rates were similar for women in the 2 dosing groups in the 1 study using standard dose (800/200 mg/day) and high dose (>800/200 mg/day) LPV/r
- The rate of preterm delivery ranged from 8.7-25.0%
- Rates of stillbirth and infant mortality were 1.0-4.8% and 0-5.8% respectively. MTCT rates were low (0-2.8%).
- In this systematic review, no unique safety or efficacy concerns were identified with the use of 400/100 mg BID LPV/r as part of HAART in pregnant women

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Disclosures

- All authors are AbbVie employees and may hold AbbVie or Abbott stock or options

- AbbVie interpreted the data, and reviewed and approved of the presentation. All authors had access to all relevant data.