

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Jourdain G, Ngo-Giang-Huong N, Harrison L, et al. Tenofovir versus placebo to prevent perinatal transmission of hepatitis B. *N Engl J Med* 2018;378:911-23. DOI: 10.1056/NEJMoa1708131

# Appendix

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## List of investigators

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**Checklist for added scrutiny for signs or conditions suggesting possible mitochondrial dysfunction**

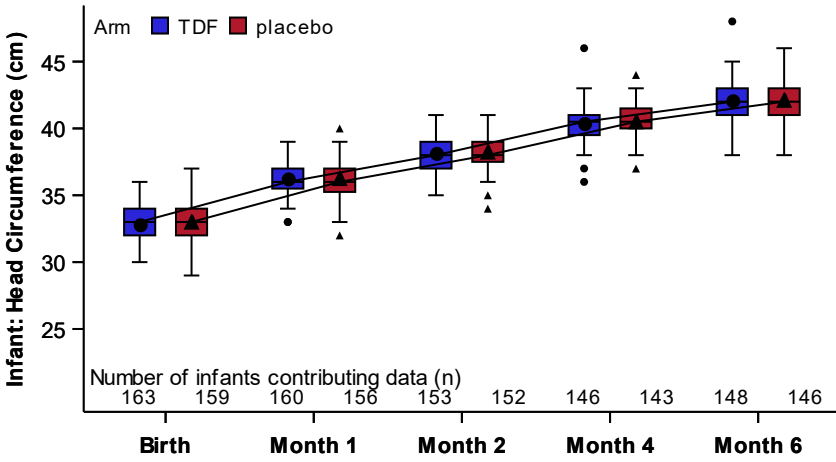
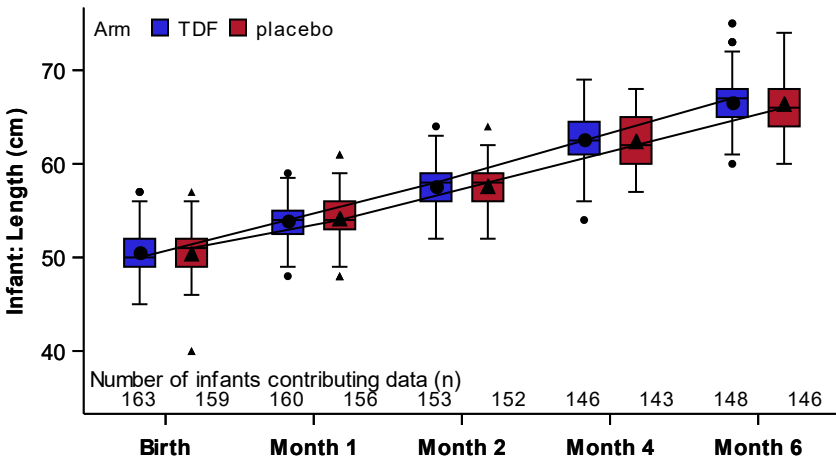
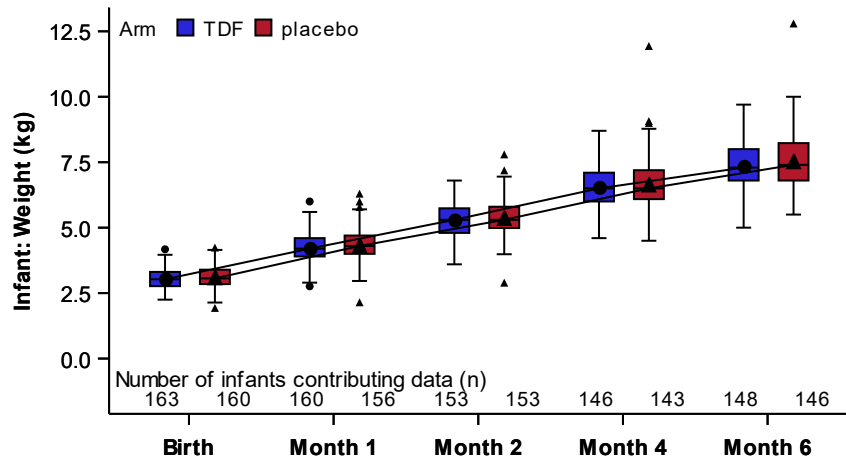
**Neurological Signs**

<b>Major signs</b>	
Non-febrile seizures, including neonatal seizures	1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No
Febrile seizures, either repeated ( $\geq 2$ episodes) or in children aged $< 6$ mths	1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No
Peripheral neuropathy	1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No
Acquired microcephaly	1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No
Cranial nerves paresis	1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No
Impaired cognitive development (for children older than 1 year)	1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No
Cerebellar dysfunction and ataxia	1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No
Motor disabilities, paraparesis, spasticity	1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No
Abnormalities on MRI or CT scan	1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No
<b>Minor signs</b>	
Febrile seizures	1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No
Isolated changes in muscular tone, hyper- and hypotonia	1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No
Behavioral disturbances and hyperactivity disorder	1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No
Hypotonia, hypertonia	1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No
Moderate cognitive delay	1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No

**Other Organs**

<b>Major signs</b>	
Pancreatitis (including biological signs)	1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No
Cardiomyopathy	1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No
Myopathy	1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No
Decrease in visual acuity, retinopathy	1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No
Abnormal ocular motor function	1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No
Nystagmus	1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No
Deafness	1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No
Unexplained death	1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No
<b>Minor signs</b>	
Increase in transaminase levels*	1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No
Persistent anemia, neutropenia or thrombopenia	1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No
Tubular defect	1 <input type="checkbox"/> Yes 0 <input type="checkbox"/> No

**Figure S1: Infant Growth over Time**



**Table S1: Women with at least one Grade 3/4 Adverse Event (AE) or Serious Adverse Event (SAE)**

Grade 3/4 AE or SAE	Randomized treatment		
	TDF (N=168)	placebo (N=163)	Total (N=331)
<b>Any grade 3/4 AE or SAE</b>	<b>41 (24%)</b>	<b>44 (27%)</b>	<b>85 (26%)</b>
<b>Investigations</b>	<b>32 (19%)</b>	<b>26 (16%)</b>	<b>58 (18%)</b>
Alanine aminotransferase increased	31 (18%)	24 (15%)	55 (17%)
Aspartate aminotransferase increased	3 (2%)	2 (1%)	5 (2%)
Blood phosphorus decreased	1 (1%)	2 (1%)	3 (1%)
<b>Pregnancy, puerperium and perinatal conditions</b>	<b>6 (4%)</b>	<b>13 (8%)</b>	<b>19 (6%)</b>
Premature labor	2 (1%)	9 (6%)	11 (3%)
Breech presentation	0 (0%)	1 (1%)	1 (<0.5%)
Stillbirth	1 (1%)	0 (0%)	1 (<0.5%)
Eclampsia	0 (0%)	1 (1%)	1 (<0.5%)
Premature rupture of membranes	1 (1%)	0 (0%)	1 (<0.5%)
False labor	0 (0%)	1 (1%)	1 (<0.5%)
Gestational hypertension	1 (1%)	0 (0%)	1 (<0.5%)
Complication of pregnancy	0 (0%)	1 (1%)	1 (<0.5%)
Postpartum hemorrhage	1 (1%)	0 (0%)	1 (<0.5%)
Retained placenta or membranes	1 (1%)	0 (0%)	1 (<0.5%)
<b>Blood and lymphatic system disorders</b>	<b>4 (2%)</b>	<b>1 (1%)</b>	<b>5 (2%)</b>
Anemia	3 (2%)	1 (1%)	4 (1%)
Lymphopenia	1 (1%)	0 (0%)	1 (<0.5%)
<b>Infections and infestations</b>	<b>0 (0%)</b>	<b>4 (2%)</b>	<b>4 (1%)</b>
Urinary tract infection	0 (0%)	2 (1%)	2 (1%)
Peritonitis	0 (0%)	1 (1%)	1 (<0.5%)
Postoperative wound infection	0 (0%)	1 (1%)	1 (<0.5%)
Endometritis decidual	0 (0%)	1 (1%)	1 (<0.5%)
<b>Injury, poisoning and procedural complications</b>	<b>1 (1%)</b>	<b>1 (1%)</b>	<b>2 (1%)</b>
Wound dehiscence	0 (0%)	1 (1%)	1 (<0.5%)
Injury	1 (1%)	0 (0%)	1 (<0.5%)
<b>Reproductive system and breast disorders</b>	<b>0 (0%)</b>	<b>1 (1%)</b>	<b>1 (&lt;0.5%)</b>
Uterine inflammation	0 (0%)	1 (1%)	1 (<0.5%)

TDF=tenofovir disoproxil fumarate

**Table S2: Infants with at least one Grade 3/4 Adverse Event (AE) or Serious Adverse Event (SAE)**

Grade 3/4 AE or SAE	Randomized treatment		
	TDF (N=161)	placebo (N=160)	Total (N=321)
<b>Any grade 3/4 AE or SAE</b>	<b>43 (27%)</b>	<b>38 (24%)</b>	<b>81 (25%)</b>
<b>Pregnancy, puerperium and perinatal conditions</b>	<b>22 (14%)</b>	<b>19 (12%)</b>	<b>41 (13%)</b>
Jaundice neonatal	18 (11%)	16 (10%)	34 (11%)
Low birth weight baby	4 (2%)	2 (1%)	6 (2%)
Premature rupture of membranes	0 (0%)	1 (1%)	1 (<0.5%)
Premature baby	0 (0%)	1 (1%)	1 (<0.5%)
<b>Infections and infestations</b>	<b>7 (4%)</b>	<b>7 (4%)</b>	<b>14 (4%)</b>
Pneumonia	3 (2%)	2 (1%)	5 (2%)
Gastroenteritis	2 (1%)	2 (1%)	4 (1%)
Respiratory tract infection	1 (1%)	1 (1%)	2 (1%)
Sepsis	0 (0%)	1 (1%)	1 (<0.5%)
Omphalitis	0 (0%)	1 (1%)	1 (<0.5%)
Diarrhea infectious	1 (1%)	0 (0%)	1 (<0.5%)
Upper respiratory tract infection	1 (1%)	0 (0%)	1 (<0.5%)
Bronchitis	0 (0%)	1 (1%)	1 (<0.5%)
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>3 (2%)</b>	<b>6 (4%)</b>	<b>9 (3%)</b>
Neonatal asphyxia	2 (1%)	3 (2%)	5 (2%)
Neonatal respiratory distress syndrome	1 (1%)	1 (1%)	2 (1%)
Meconium aspiration syndrome	0 (0%)	1 (1%)	1 (<0.5%)
Transient tachypnoea of the newborn	0 (0%)	1 (1%)	1 (<0.5%)
<b>Blood and lymphatic system disorders</b>	<b>4 (2%)</b>	<b>4 (3%)</b>	<b>8 (2%)</b>
Leukocytosis	2 (1%)	4 (3%)	6 (2%)
Anemia	1 (1%)	0 (0%)	1 (<0.5%)
Neutropenia	1 (1%)	0 (0%)	1 (<0.5%)
<b>Hepatobiliary disorders</b>	<b>6 (4%)</b>	<b>1 (1%)</b>	<b>7 (2%)</b>
Hyperbilirubinemia neonatal	5 (3%)	0 (0%)	5 (2%)
Jaundice	1 (1%)	1 (1%)	2 (1%)
<b>Investigations</b>	<b>2 (1%)</b>	<b>3 (2%)</b>	<b>5 (2%)</b>
Treponema test positive	1 (1%)	2 (1%)	3 (1%)
Neutrophil count abnormal	0 (0%)	1 (1%)	1 (<0.5%)
Alanine aminotransferase increased	1 (1%)	0 (0%)	1 (<0.5%)
<b>Congenital, familial and genetic disorders</b>	<b>4 (2%)</b>	<b>1 (1%)</b>	<b>5 (2%)</b>
Glucose-6-phosphate dehydrogenase deficiency	2 (1%)	0 (0%)	2 (1%)
Congenital anomaly	1 (1%)	1 (1%)	2 (1%)
Talipes	1 (1%)	0 (0%)	1 (<0.5%)
<b>General disorders and administration site conditions</b>	<b>1 (1%)</b>	<b>2 (1%)</b>	<b>3 (1%)</b>
Pyrexia	1 (1%)	2 (1%)	3 (1%)
<b>Immune system disorders</b>	<b>0 (0%)</b>	<b>1 (1%)</b>	<b>1 (&lt;0.5%)</b>
Milk allergy	0 (0%)	1 (1%)	1 (<0.5%)
<b>Metabolism and nutrition disorders</b>	<b>0 (0%)</b>	<b>1 (1%)</b>	<b>1 (&lt;0.5%)</b>
Hypoglycemia	0 (0%)	1 (1%)	1 (<0.5%)

TDF=tenofovir disoproxil fumarate, CI=confidence interval

Infants from multiple pregnancies are counted as one mother-infant(s) pair in the denominator, and all AEs in any infant are displayed.