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CHU Saint-Pierre
UMC Sint-Pieter

Les enfants exposés in utero au VIH et non infectés

Le nouveau challenge dans le domaine du VIH pédiatrique

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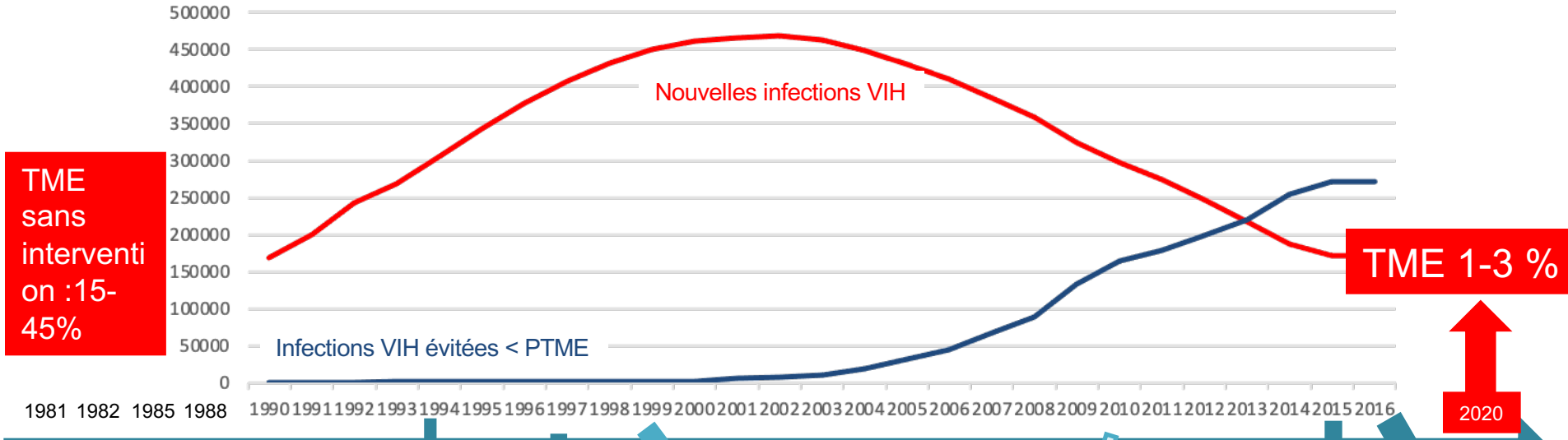
AFRANUM
Modules de formation numérique AFRAVIH

Jeudi 20 avril 2023

Historique des mesures de prévention



TME sans interventi on :15-45%

TME 1-3 %

SIDA

PACTG076

Tt combinant 3 ARV

césarienne

AM autorisée

Option B+ OMS
ARV pour toutes les ♀ enceintes HIV+

Tt universel

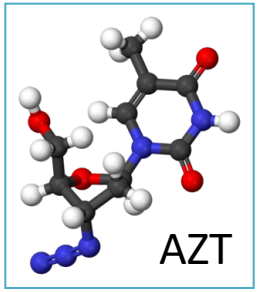
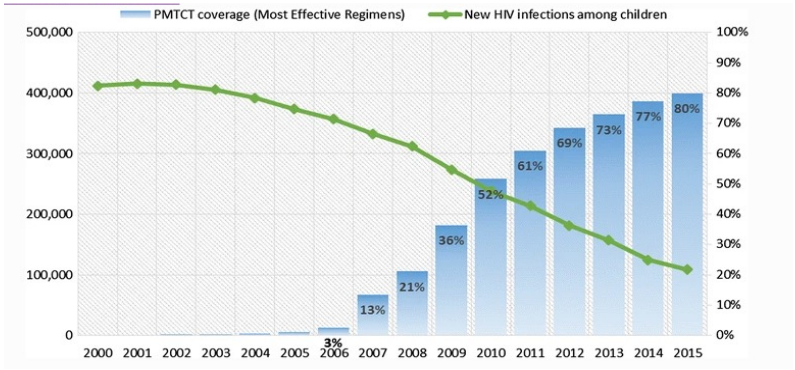
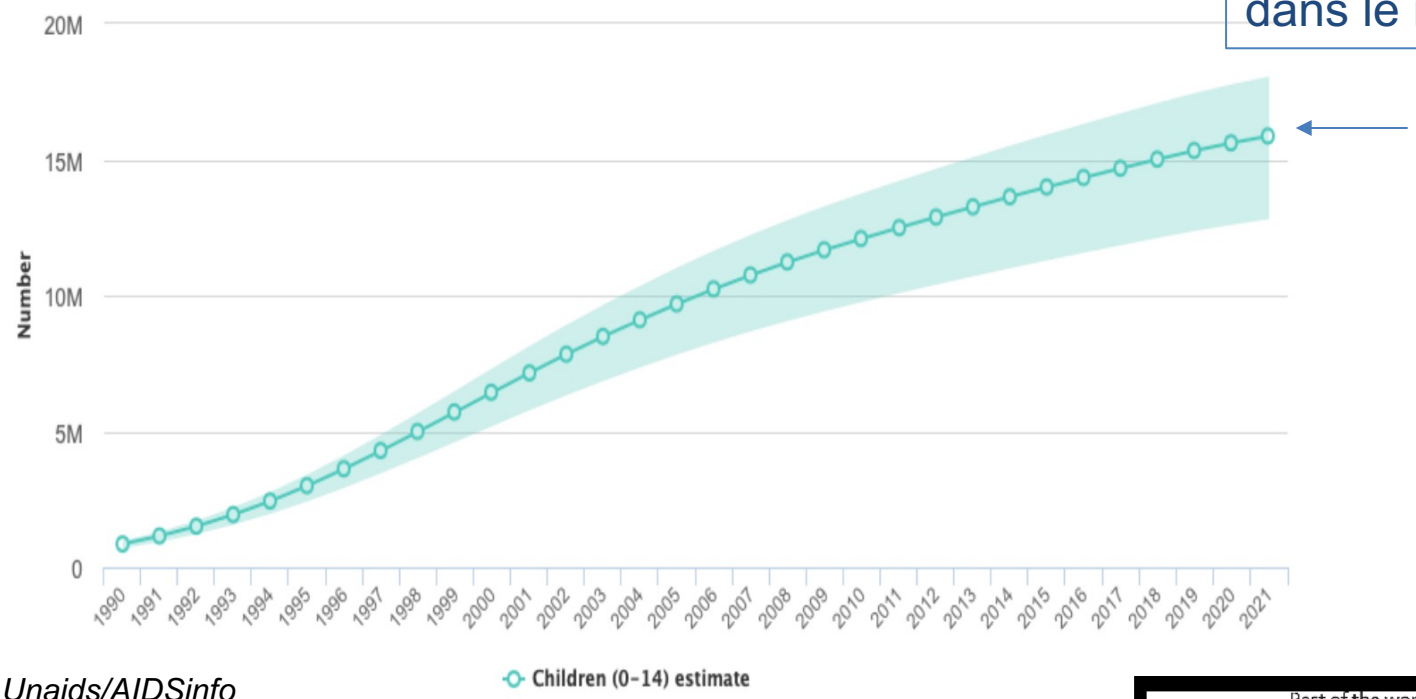


TABLE 1. Pediatric AIDS Clinical Trials Group (PACTG) 076 zidovudine (ZDV) regimen

Time of ZDV administration	Regimen
Antepartum	Oral administration of 100 mg ZDV five times daily,* initiated at 14–34 weeks' gestation and continued throughout the pregnancy.
Intrapartum	During labor, intravenous administration of ZDV in a 1-hour initial dose of 2 mg/kg body weight, followed by a continuous infusion of 1 mg/kg body weight per hour until delivery.
Postpartum	Oral administration of ZDV to the newborn (ZDV syrup at 2 mg/kg body weight/dose every 6 hours) for the first 6 weeks of life, beginning at 8–12 hours after birth.†

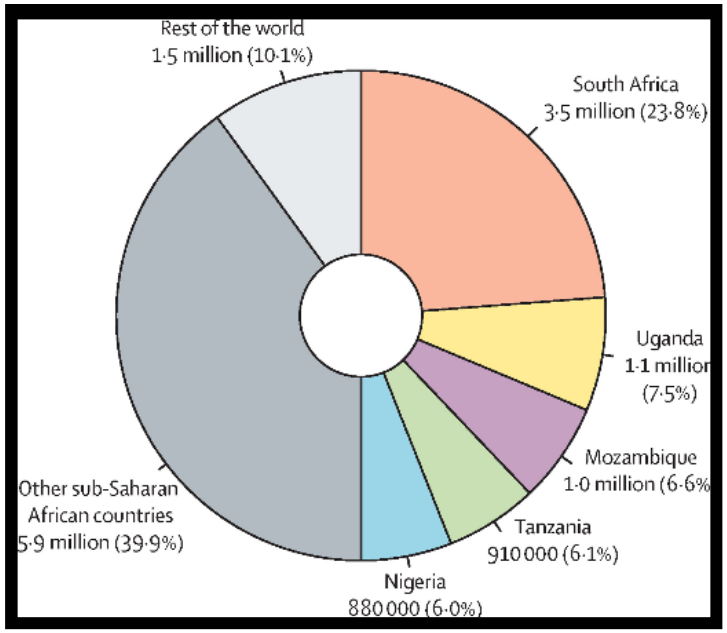


Nombre d'enfants HEU dans le monde



Unaids/AIDSinfo

Estimations ONUSIDA de la contribution de chaque pays (%) à la population mondiale d'enfants HEU en 2018



Survie et développement des enfants exposés moins optimal >< enfants non exposés

Les enfants exposés non infectés : le nouveau challenge dans le domaine du VIH pédiatrique?

Mortalité et morbidité accrue liée aux infections

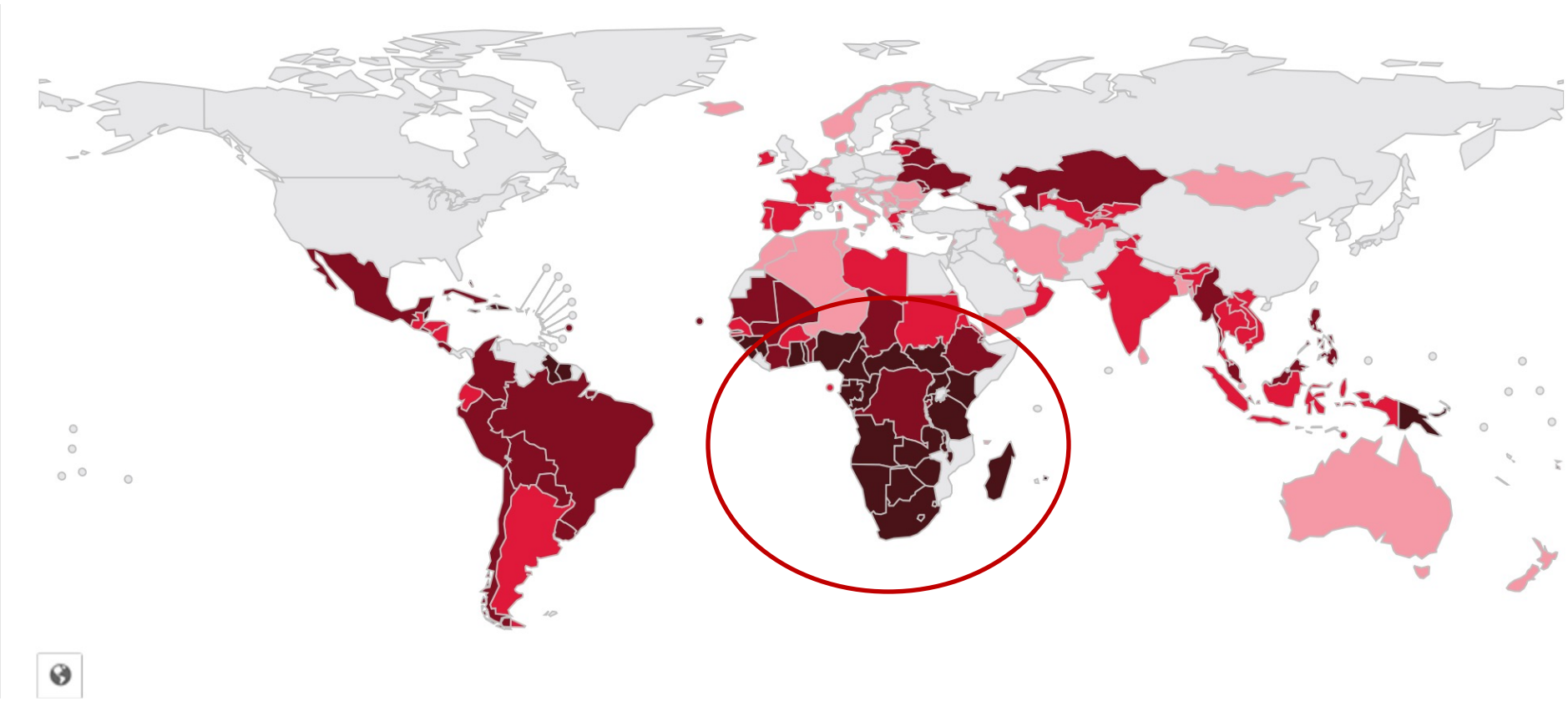
Développement neurologique: Retard de langage, TSA, …

Mécanismes impliqués: complexe et multifactoriels

Impact de l'exposition au VIH/ARV

Inspired by Afran, CEI,2013

Morbidité et mortalité accrue



Les 1ères études datent de l'ère pré-traitement ARV et proviennent essentiellement des pays d'Afrique sub-saharienne

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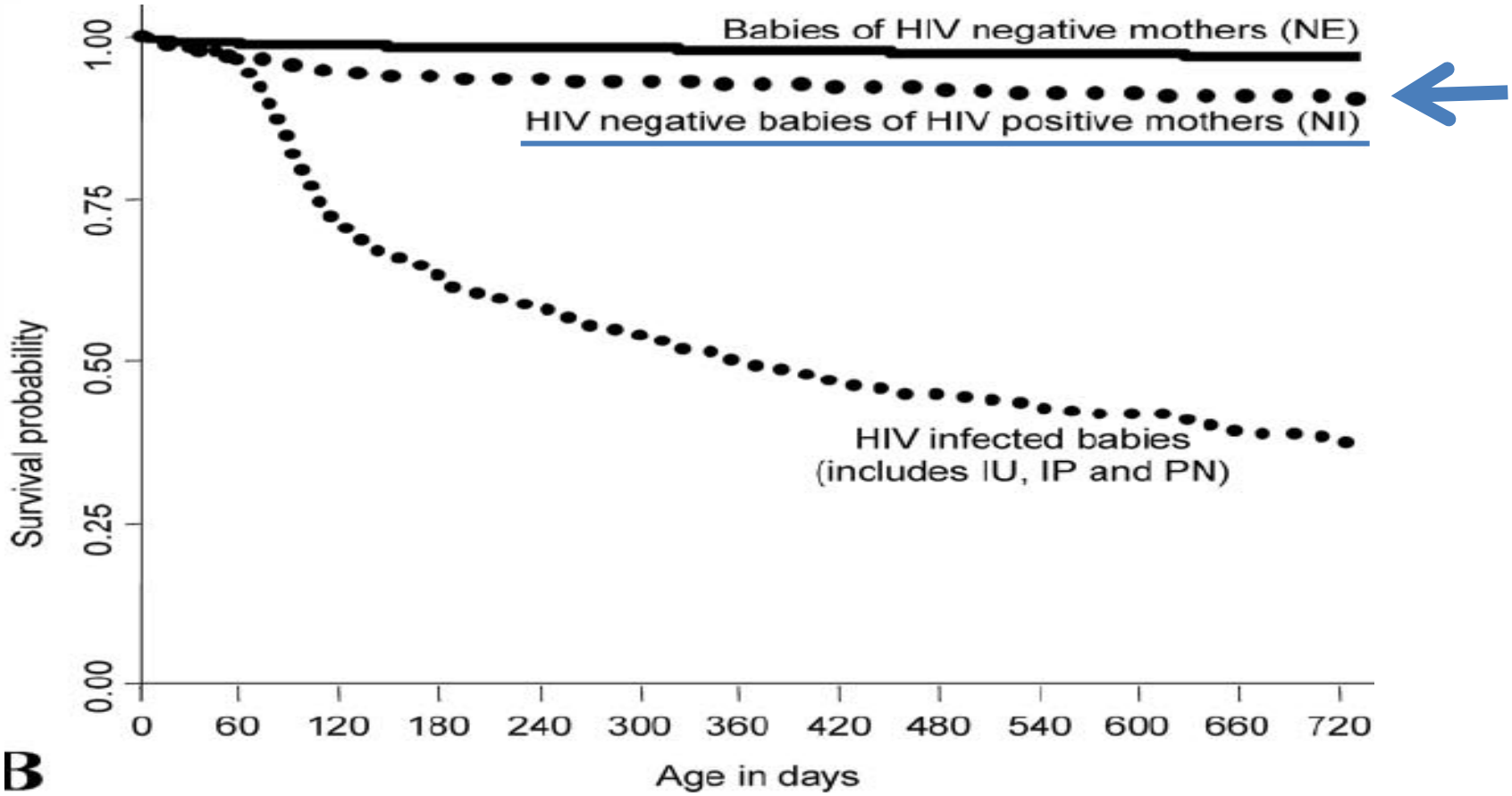
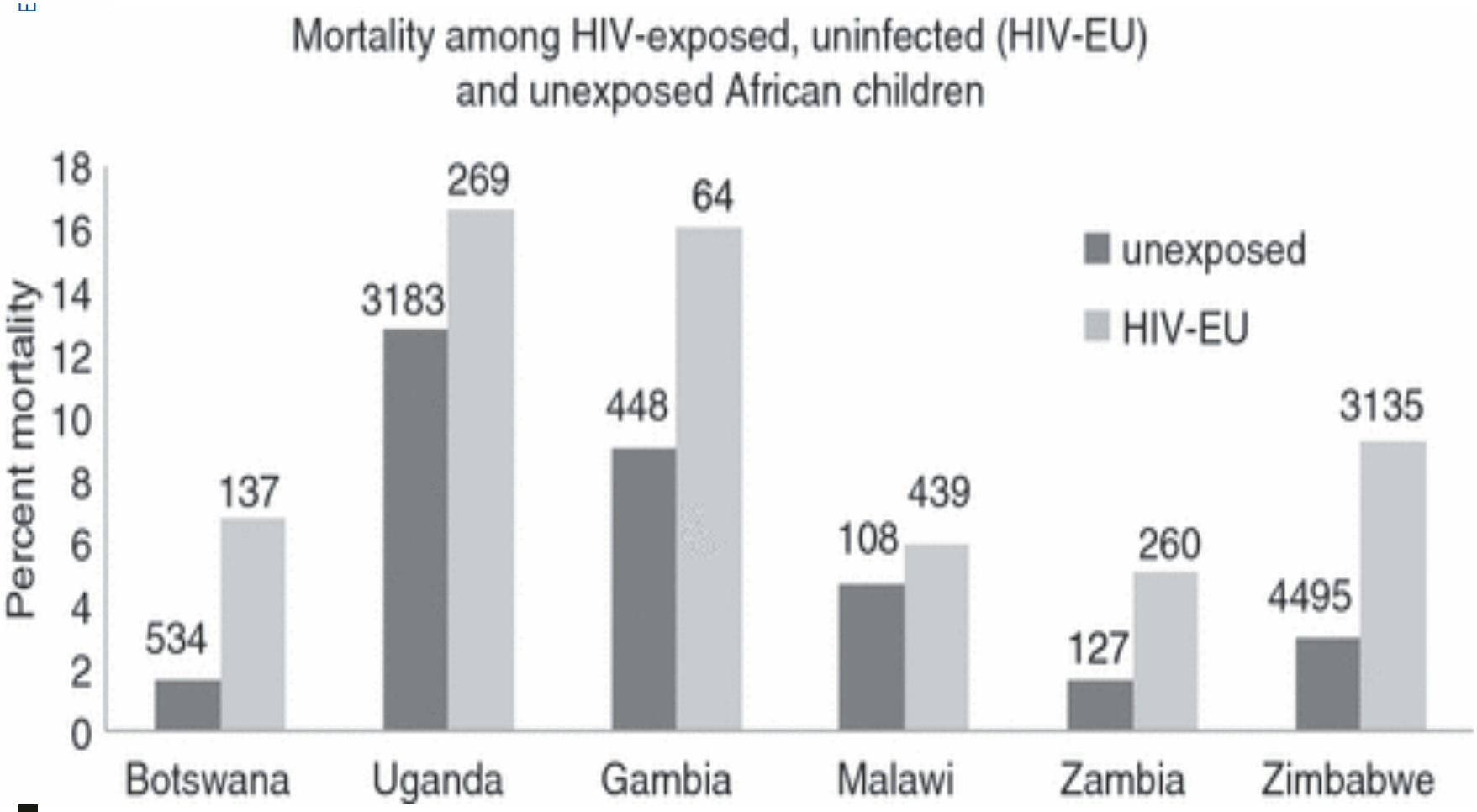
Child Mortality According to Maternal and Infant HIV Status in Zimbabwe

Edmore Marinda, MSc, Jean H. Humphrey, ScD,† Peter J. Iliff, MRCPCH,* Kuda Mutasa, BSc,* Kusum J. Nathoo, MRCP,‡ Ellen G. Piwoz, ScD,§ Lawrence H. Moulton, PhD,† Peter Salama, MD, MPH,‖ Brian J. Ward, MD,¶ and the ZVITAMBO Study Group*



Marinda, PIDJ 2007

The HIV-exposed, uninfected African child



Tropical Medicine & International Health
Volume 14, Issue 3, pages 276-287, 20 JAN 2009 DOI: 10.1111/j.1365-3156.2009.02220.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-3156.2009.02220.x/full#f1

Mortalité des HEU

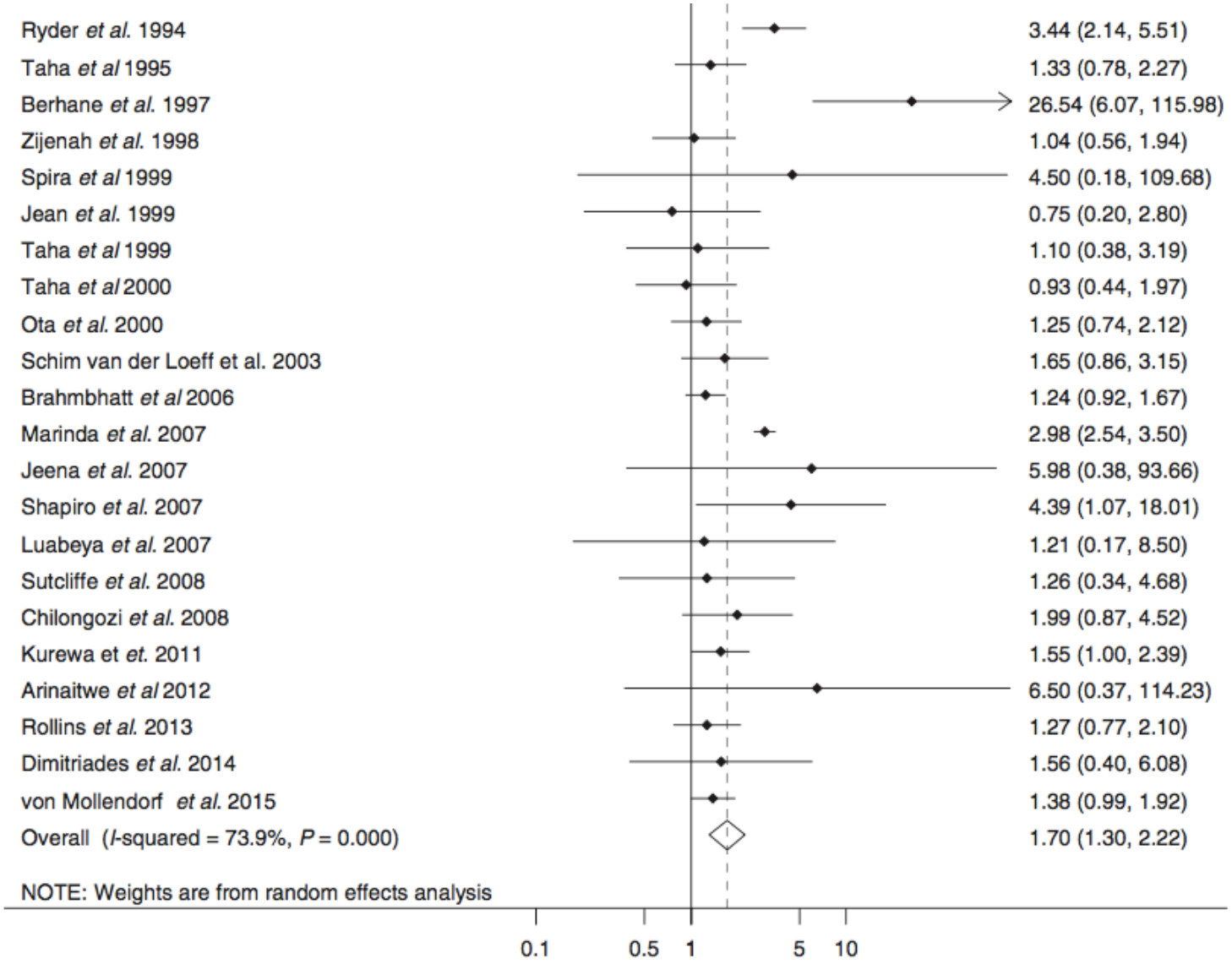
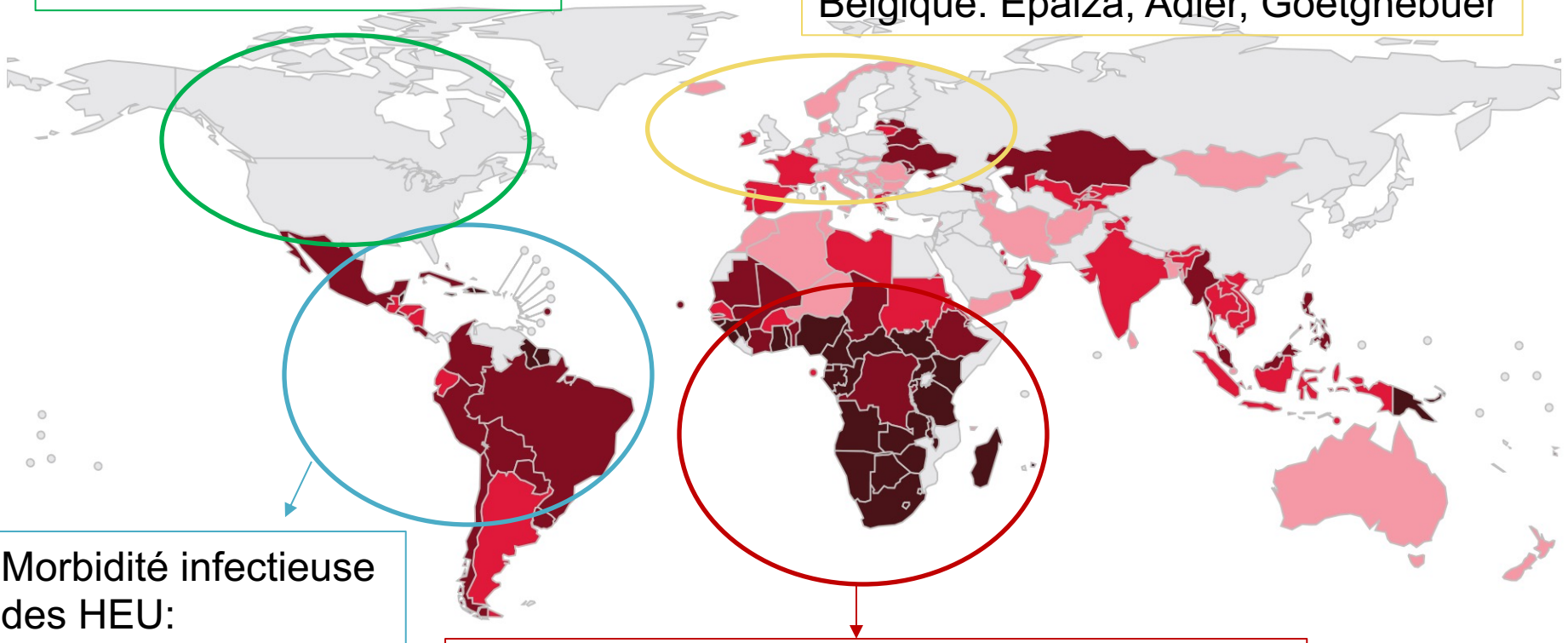


Fig. 2. Forest plot of risk ratios for mortality comparing HIV-exposed uninfected to HIV-unexposed uninfected children for all studies ($n = 22$).

Brennan et al, AIDS 2016, Vol 30 No 15

US: Paul, Labuda
Québec: Wizman, Lamarre

Royaume Unis: Newell, Thorne
France: Taron-Brocart
Belgique: Epalza, Adler, Goetghebuer



Morbidité infectieuse des HEU:
-Infections respiratoires ++
- Mussi-Pinhata and al, Weinberg and al

1ère études avant l'ère des ARV:
- Mortalité accrue des enfants HEU >< HUU
- Marinda and al, Filteau, Slogrove and al

Revue plus récente , post-ère des ARV
- Mortalité > des HEU
- Brennan and al

Développement neurologique

- Études réalisés avant l'ère du Tt universel
  - Association entre exposition au VIH et trouble du neurodéveloppement
  - Effets variables de l'exposition au VIH selon les pays
    - Gravité de la maladie de la mère / Exposition aux ARV
- Études de l'ère du Tt universel : résultats discordants
- Retard d'acquisition du langage
  - Certains ARV (atazanavir)

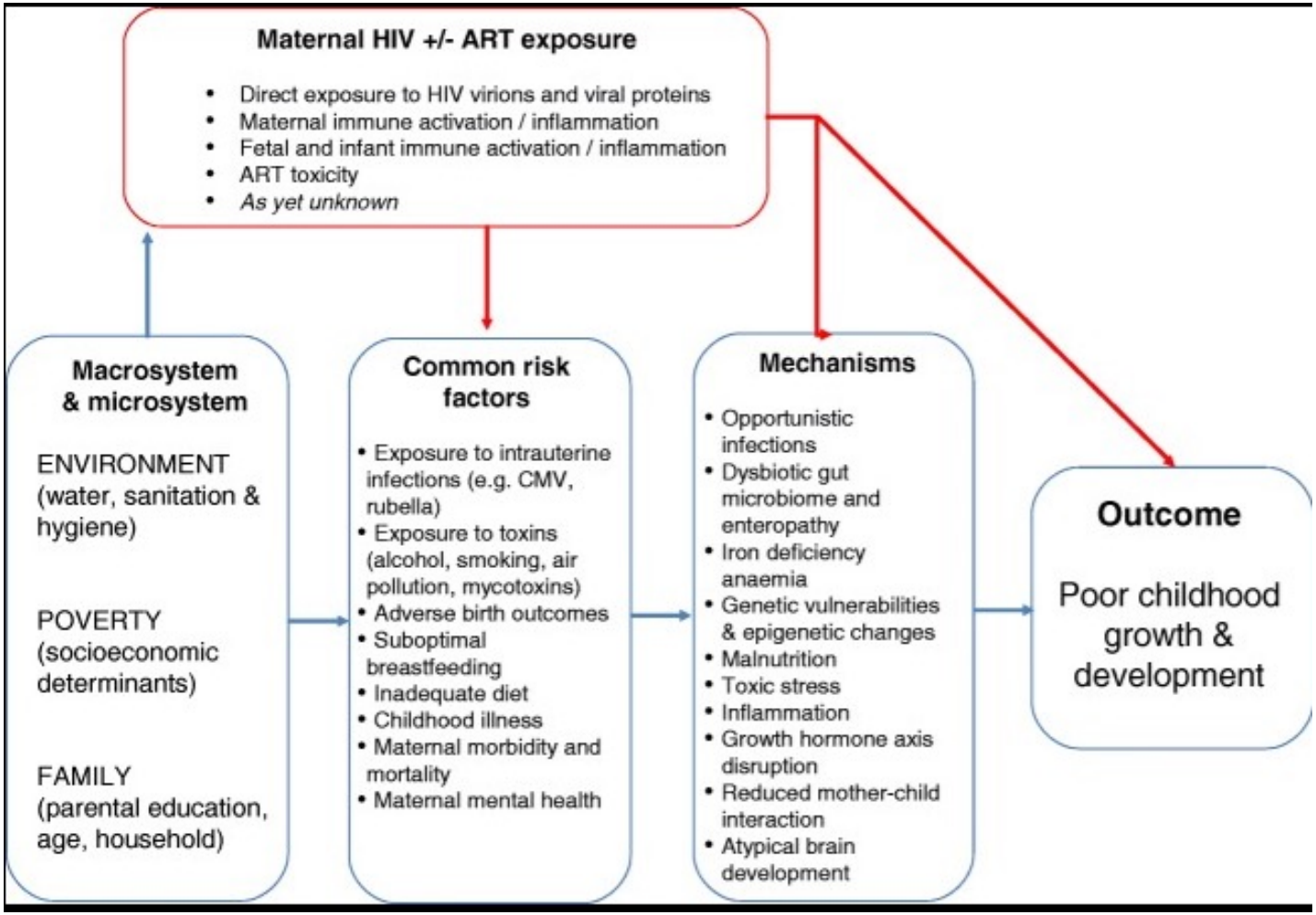
Evaluation of Risk for Late Language Emergence After In Utero Antiretroviral Drug Exposure in HIV-exposed Uninfected Infants

Mabel L. Rice, PhD, Bret Zeldow, MS,† George K. Siberry, MD, MPH,‡ Murli Purswani, MD,§ Kathleen Malee, PhD,¶ Howard J. Hoffman, MA,|| Toni Frederick, PhD, MSPH,** Ashley Buchanan, MS,† Patricia A. Sirois, PhD,†† Susannah M. Allison, PhD,‡‡ and Paige L. Williams, PhD,† for the Pediatric HIV/AIDS Cohort Study (PHACS)*

PIDJ 2013; 32(10):e406-413

- Evaluation de l'incidence du retard de langage à 1 et 2 ans chez 792 HEU enfants exposés non infectés
- Incidence de retard = 26% à 1 an and 23% à 2 ans
- Facteurs de risque:
  - administration d'ATV pendant le troisième trimestre

Hypothèses de causalité



Weddeburn et al, Curr HIV/AIDS Reports 2019; 16(6):501-13

Effets secondaires des ARV

- Naissance prématurée / dysmaturité
- Malformations congénitales
- Anémies, Cytopénies
- Anomalies mitochondriales / Acidose lactique

Perinatal outcomes associated with combination antiretroviral therapy compared with monotherapy

Clara Portwood[a], Harriet Sexton[a], Mary Kumarendran[a], Zoe Brandon[a], Bradley Johnson[a], Shona Kirtley[b] and Joris Hemelaar[a]

Objectives: Increasing numbers of women living with HIV (WLHIV) worldwide receive combination antiretroviral therapy (cART) during pregnancy. We aimed to assess the risk of adverse perinatal outcomes in pregnant WLHIV receiving cART compared with pregnant WLHIV receiving zidovudine monotherapy.

Design: Systematic review and meta-analysis.

Methods: We searched four electronic literature databases (PubMed, CINAHL, Global Health, EMBASE) for studies published between 1 January 1980 and 20 April 2020 using a comprehensive search strategy. Studies reporting data on WLHIV receiving cART compared with WLHIV receiving monotherapy for 11 adverse perinatal outcomes were sought: preterm birth (PTB), very PTB, spontaneous PTB, low birthweight (LBW), very LBW, preterm and term LBW, small for gestational age (SGA), very SGA (VSGA), stillbirth, and neonatal death. Random-effects meta-analyses were conducted to calculate relative risk (RR) and 95% confidence intervals (95% CI).

Results: We included 30 studies reporting on 317 101 pregnant women in 27 countries. WLHIV receiving cART were at increased risk of PTB (RR 1.32, 95% CI 1.18–1.46), LBW (1.35, 1.19–1.53), SGA (1.32, 1.13–1.53), VSGA (1.64, 1.34–2.02), and stillbirth (2.41, 1.83–3.17) compared to WLHIV receiving monotherapy. The significance of these results was maintained in subgroup analyses for studies conducted in low and middle-income countries and average quality studies. Additionally, WLHIV receiving nonnucleoside reverse transcriptase inhibitor-based cART were associated with increased risk of PTB, LBW, and stillbirth, while WLHIV receiving protease inhibitor-based cART were associated with increased risk of PTB, compared with WLHIV receiving monotherapy.

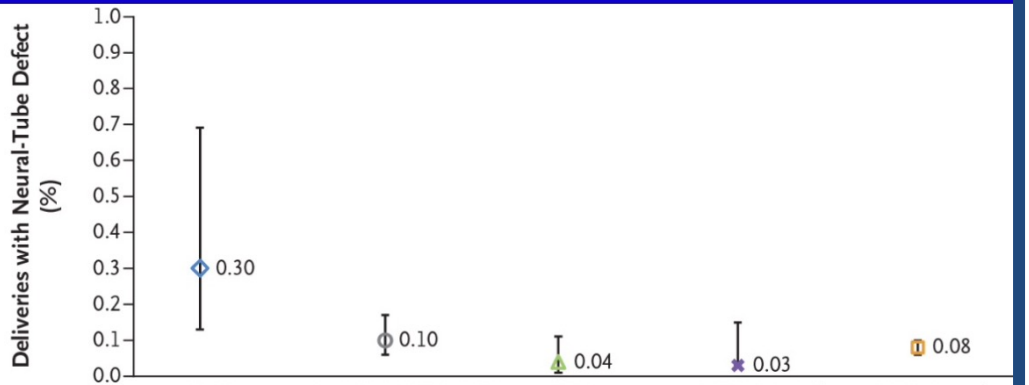
Conclusion: Pregnant WLHIV receiving cART are associated with increased risk of adverse perinatal outcomes, compared with WLHIV receiving monotherapy.

AIDS 2023, **37**:489–501

N Engl J Med. 2019 Aug 29;381(9):827-840. doi: 10.1056/NEJMoa1905230. Epub 2019 Jul 22.

Neural-Tube Defects and Antiretroviral Treatment Regimens in Botswana

Rebecca Zash [1], Lewis Holmes [1], Modiegi Diseko [1], Denise L Jacobson [1], Sean Brummel [1], Gloria Mayondi [1], Arielle Isaacson [1], Sonya Davey [1], Judith Mabuta [1], Mompati Mmalane [1], Tendani Gaolathe [1], M Essex [1], Shahin Lockman [1], Joseph Makhema [1], Roger L Shapiro [1]



	DTG at Conception	Any Non-DTG ART at Conception	EFV at Conception	DTG Started during Pregnancy	HIV-Negative
No. of Neural-Tube Defects	5	15	3	1	70
No. of Exposures	1683	14,792	7959	3840	89,372
Percent with Defect (95% CI)	0.30 (0.13–0.69)	0.10 (0.06–0.17)	0.04 (0.01–0.11)	0.03 (0.00–0.15)	0.08 (0.06–0.10)
Difference in Prevalence (95% CI) — Percentage Points	Reference	0.20 (0.01–0.59)	0.26 (0.07–0.66)	0.27 (0.06–0.67)	0.22 (0.05–0.62)

Conclusions: The prevalence of neural-tube defects was slightly higher in association with dolutegravir exposure at conception than with other types of ART exposure at conception (3 per 1000 deliveries vs. 1 per 1000 deliveries). (Funded by the National Institutes of Health.).

Lancet 1999; 354 (25):1084-9

Early report

Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues

Stéphane Blanche, Marc Tardieu, Pierre Rustin, Abdelhamid Slama, Béatrice Barret, Ghislaine Firtion, Nicole Ciraru-Vigneron, Catherine Lacroix, Christine Rouzioux, Laurent Mandelbrot, Isabelle Desguerre, Agnès Rötig, Marie-Jeanne Mayaux, Jean-François Delfraissy

- 8 enfants présentant anomalies mitochondriales incluant
  - 5 maladies neurologiques (2 décès)
  - 3 developpement normal mais biologie anormale
- 5 enfants avec dysfonctionnement complet de la chaine respiratoire

Persistent mitochondrial dysfunction in HIV-1-exposed but uninfected infants: clinical screening in a large prospective cohort
Barret et al, EPF. AIDS 2003,17:1769-85

4392 Enfants exposés non infectés

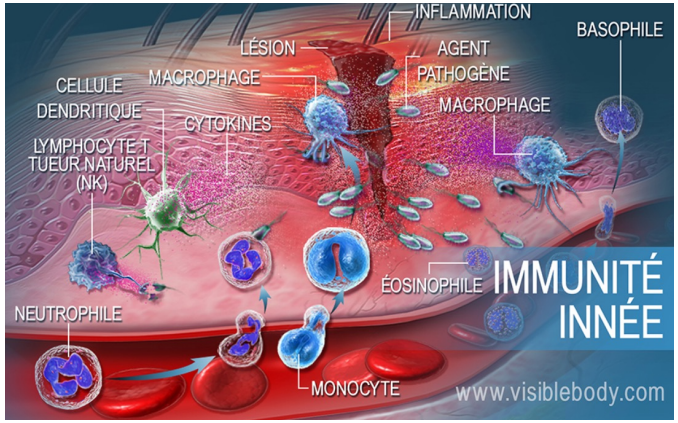
Incidence de mitochondriopathie à 18 mois= 0.26% [0.10-0.54]
vs 0,01% dans la population générale

Hypothèses pour expliquer la susceptibilité aux infections

- Facteurs de risques:
  - Milieu socio-économique défavorisé
  - Environnement infectieux
  - Prématurité
  - Absence d'allaitement maternel

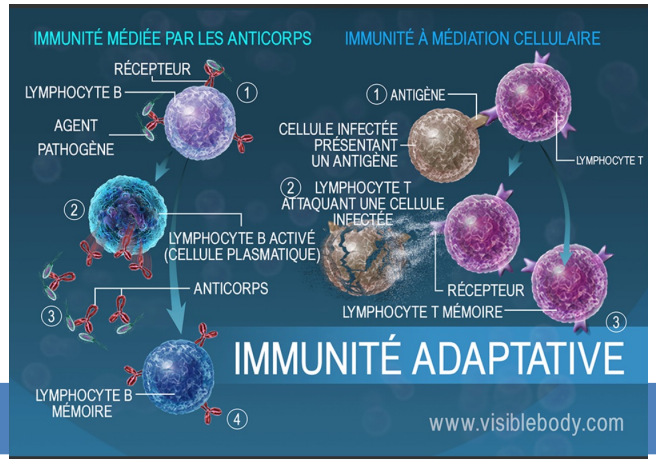
- Altération des réponses immunitaires
  - Innées
  - Adaptatives

Réponses immunitaires innées



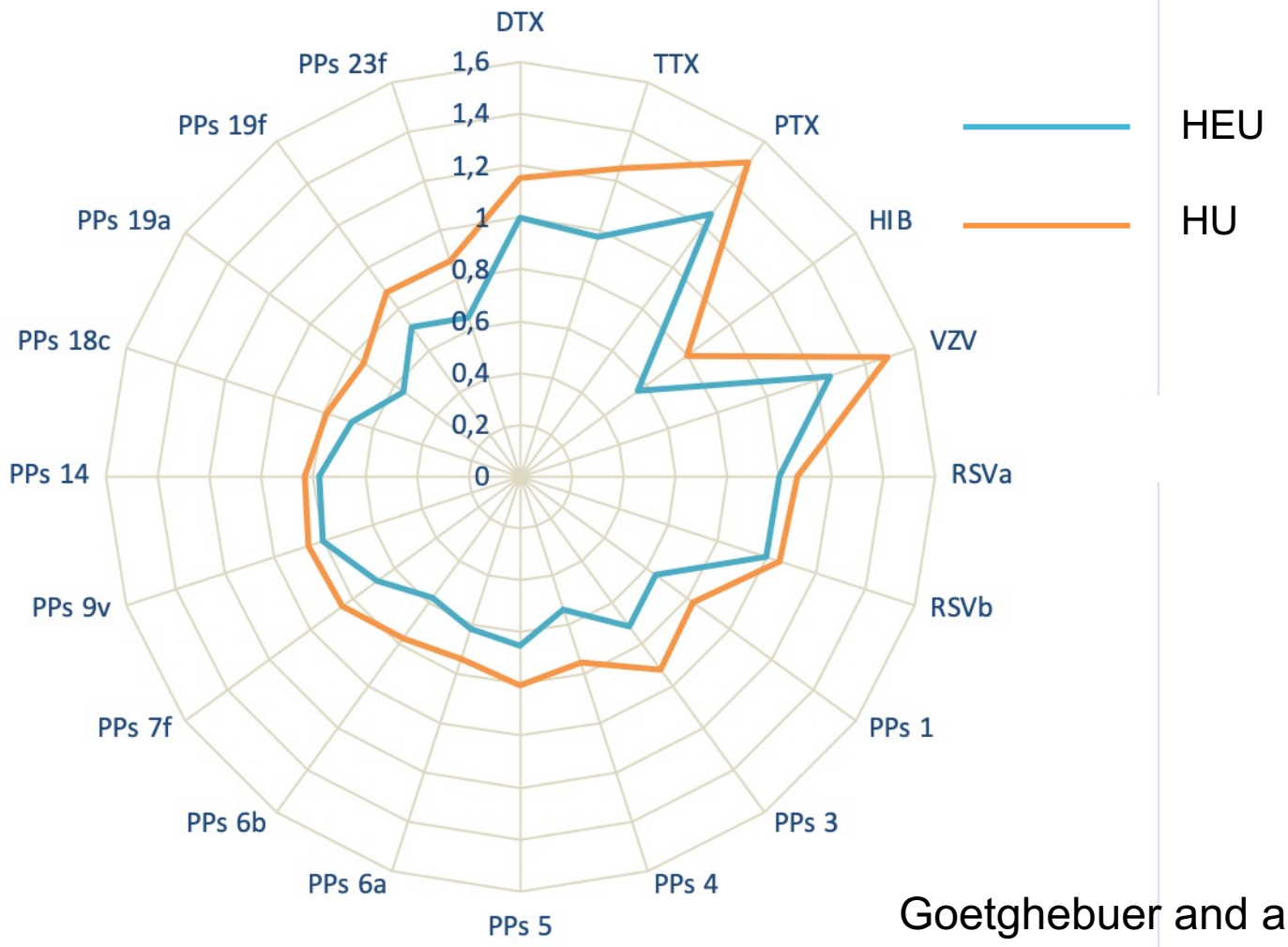
Activation immune (A.I) chronique maternel	Monocytes activés C/° nn Profil cytokinique modifié	Brenchley 2006 Lohman-Payne 2018 Goetghebuer 2019
Altération du microbiome intestinal maternel	Translocation microbienne et activation immune du nourrisson	Bender 2016 Jackson 2022
Exposition aux ARVs	An. des paramètres hématologiques • PN • Monocytes activés – TNF-α • Cellules NK • Cellules dendritiques	Abu-Raya 2016 Reikie 2014 Dirajlal-Fargo 2019 Slyker 2012

Réponses immunitaires adaptatives



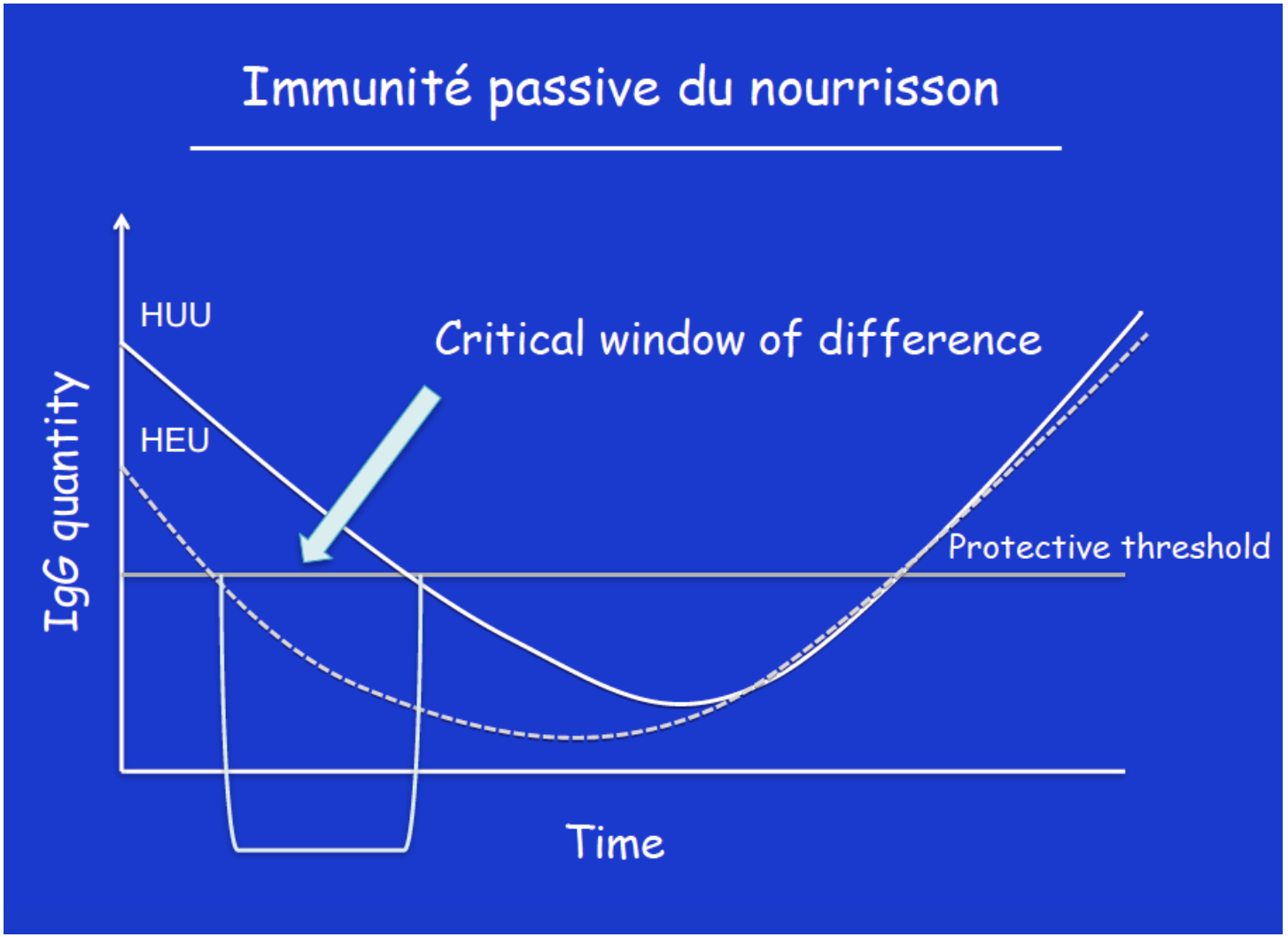
Thymopoièse et altération de la fonction thymique	Brito-Pérez 2021 Clerici 2000 Nielsen 2001
Activation des lymphocytes T CD8+	Miyamoto 2017
Réponses vaccinales moins efficaces < BCG et toxine tétanique	Jalbert 2019 Garcia-Knight 2015
Transfert réduit d'Ac maternels	Weinberg, 2017 Goetghebuer, 2019 Patel, 2020

Transfert réduit d'Ac maternels chez les HEU



Goetghebuer and al, 2019

Risque d'infections sévères essentiellement la première année de vie



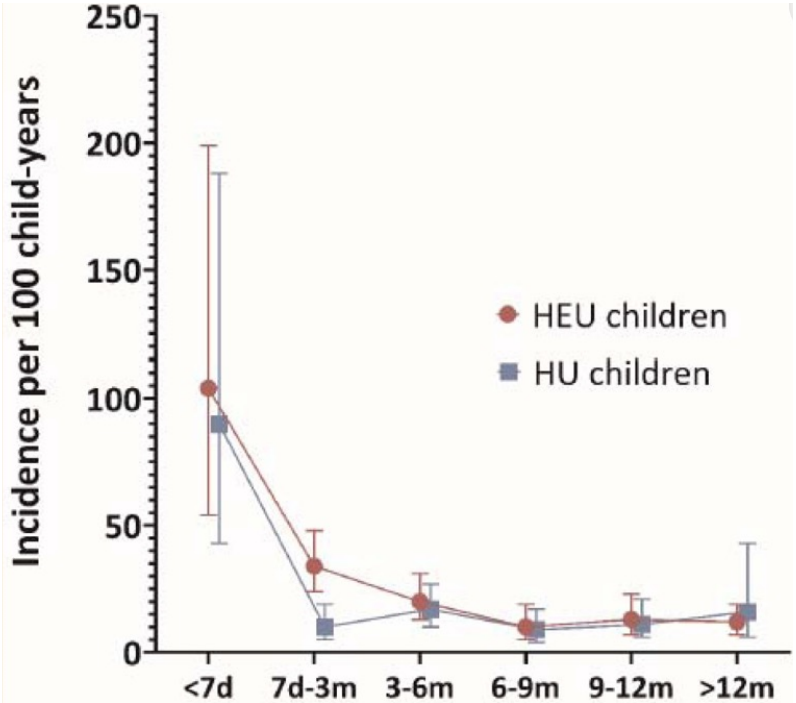
Infectious morbidity of breastfed, HIV-exposed uninfected infants under conditions of universal antiretroviral therapy in South Africa: a prospective cohort study

Lancet Child Adolesc Health 2020;4(3):220-31

	HEU (n=459)	HU (n=410)	p-value
Completed secondary education	113 (25%)	184 (45%)	<0,0001
Employed	182 (40%)	194 (47%)	0,023
Flush toilets inside home	125 (27%)	165 (40%)	<0,0001
Running water inside home	188 (41%)	214 (52%)	0,001
Household crowding (>9 people)	28 (6%)	12 (3%)	0,026
Risky drinking	116 (25%)	30 (7%)	<0,0001
Intimate partner violence	101 (22%)	32 (8%)	<0,0001

Infectious morbidity of breastfed, HIV-exposed uninfected infants under conditions of universal antiretroviral therapy in South Africa: a prospective cohort study

Lancet Child Adolesc Health 2020;4(3):220-31

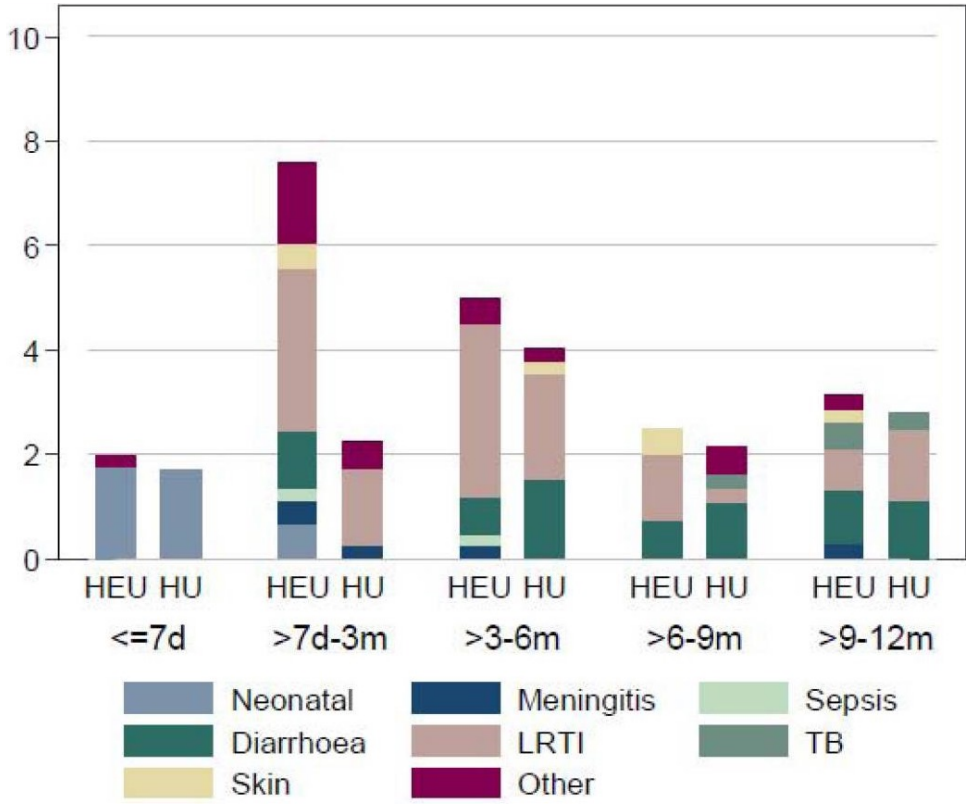


	<7d	7d-3m	3-6m	6-9m	9-12m	>12m
Crude IRR (95% CI)	1.16 (0.43-3.08)	3.50 (1.68-7.28)	1.21 (0.59-2.49)	1.16 (0.46-2.90)	1.15 (0.50-2.62)	0.71 (0.23-2.16)
Adjusted IRR (95% CI)	1.14 (0.43-3.03)	3.49 (1.68-7.27)	1.12 (0.53-2.35)	1.30 (0.55-3.10)	1.45 (0.61-3.44)	0.47 (0.17-1.26)

Infection-related hospitalization: incidence rates and rate ratios comparing HIV-exposed uninfected to HIV-unexposed children over time

Infectious morbidity of breastfed, HIV-exposed uninfected infants under conditions of universal antiretroviral therapy in South Africa: a prospective cohort study

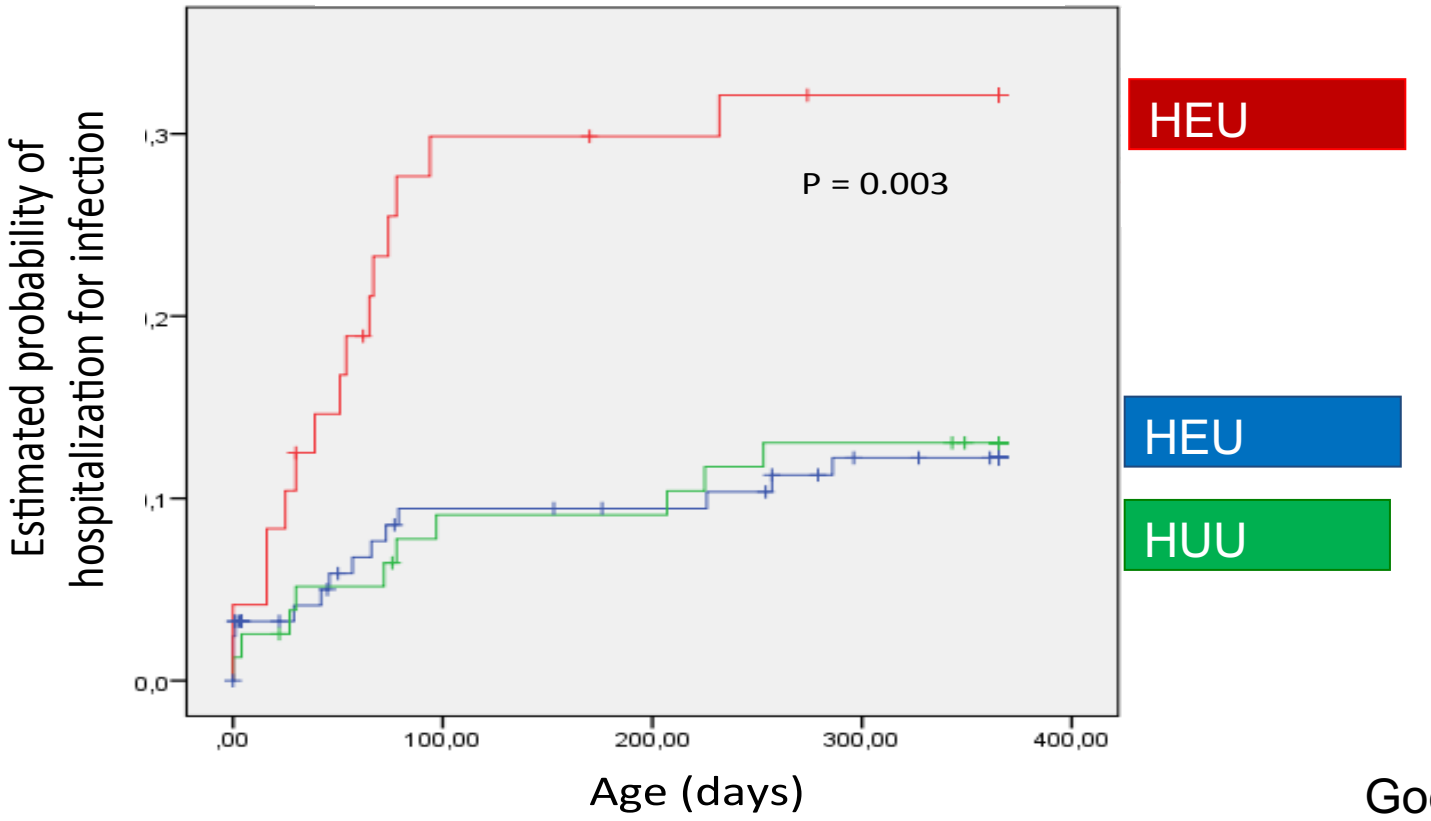
Lancet Child Adolesc Health 2020;4(3):220-31



Infection-related causes for hospitalization: distribution by HIV exposure and age category

Le contrôle de la maladie maternelle = facteur protecteur

Initiation of ARV during pregnancy is a major risk factor of hospitalization for infection in HEU infants



Goetghebuer, 2019

Messages Clés:

- **Élimination virtuelle de la transmission du VIH**
  - Efficacité des mesures de prévention
- **Enfants non infectés mais restent « affectés » par le VIH**
  - Mortalité / morbidité infectieuse accrue
    - Essentiellement avant l'âge d'un an
  - Développement neurologique peut être altéré
- **Facteurs de risque**
  - liés au VIH
  - universels majorés par le VIH
- Importance du **contrôle de la maladie maternelle avant la grossesse**

Prise en charge spécifique des enfants exposés au VIH :

- Contrôle de la maladie maternelle
- Choix des ARV
- Préventions des infections congénitales -CMV
- Prise en charge psychologique
- Prise en charge précarité sociale
- Follow up attentif
- Vaccinations
- Test neuro-developpemental à 18 mois