Symposium du CMIT

Jeudi 6 octobre 2022

Jean-François FAUCHER

CHU Limoges

La résistance se joue des frontières

Paludisme résistant aux dérivés de l'artémisinine

- Un cas de paludisme d'importation
- Séjour en Thaïlande (1 mois), puis en Ouganda (2 mois) ; pas de chimioprophylaxie
- Paludisme grave d'importation en France traité par artésunate IV
- Décroissance parasitémie d'un **facteur 37 en 56 heures**:

  765 000 trophozoïtes/µL (H0)

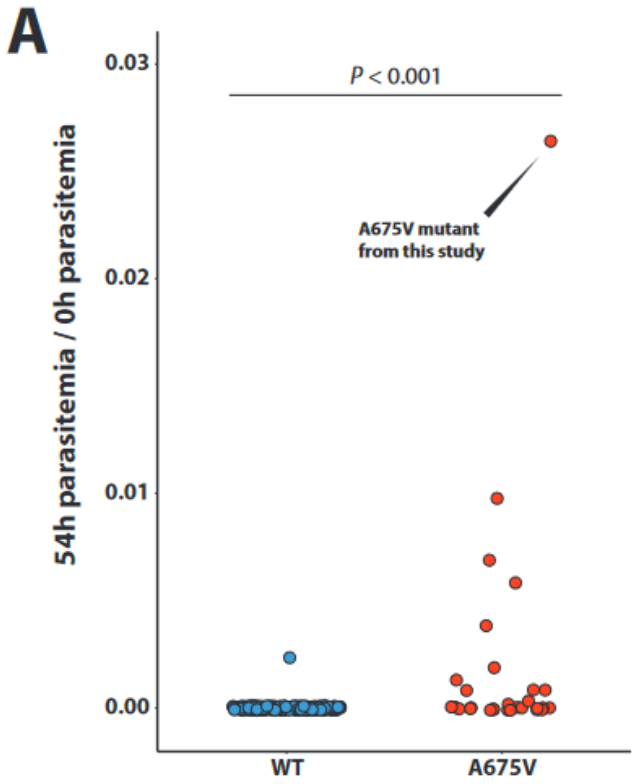
  20 250 trophozoïtes/µL (H56)

- Mutation A675V (kelch13)
  - de Thaïlande ou d'Ouganda?

Clinical Infectious Diseases® 2022;75(7):1242–4

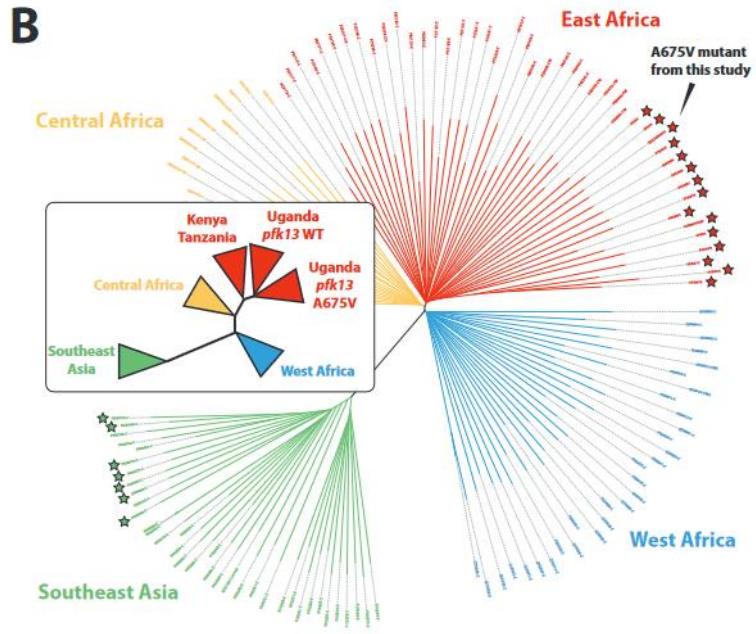
Paludisme résistant aux dérivés de l'artémisinine

- Mutation A675V (kelch13)
- Ouganda (229): H54
  - 201 « **sauvages** »: 1 (0,5%)
  - 28 souches **A675V**: 10 (37%)



Paludisme résistant aux dérivés de l'artémisinine

- Séquençage de la souche isolée chez le voyageur
- La souche venait d'Afrique!
- Voyages: propagation potentielle de résistance

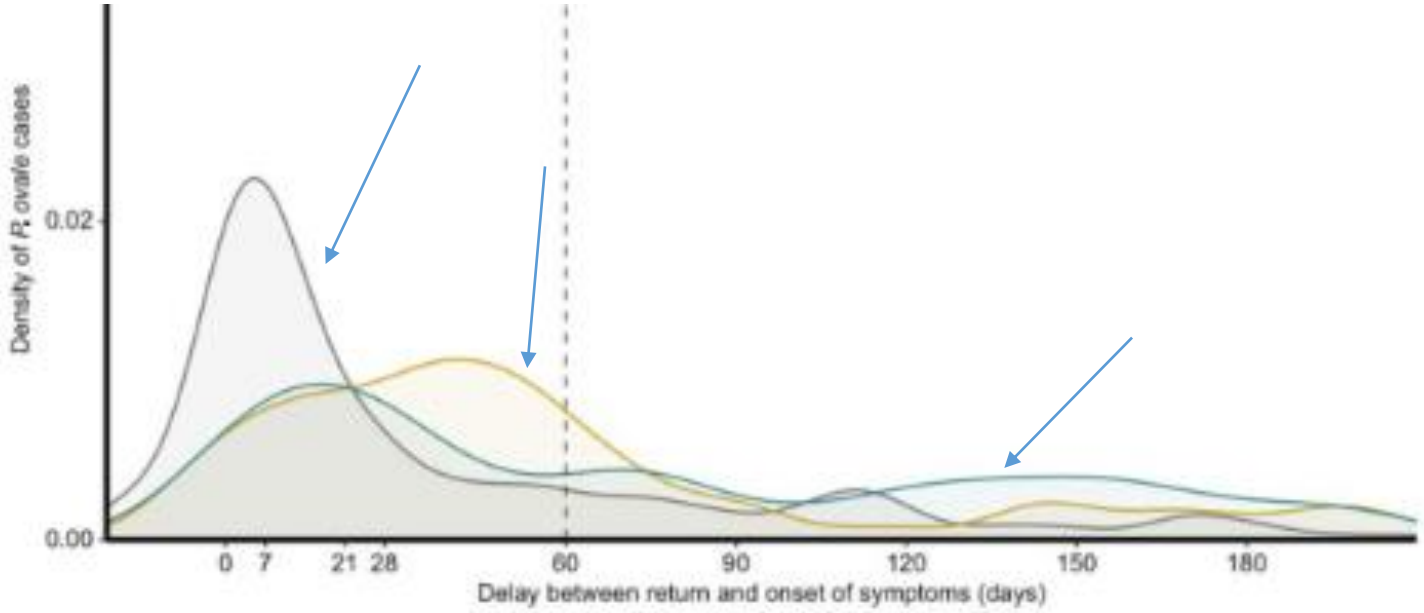


Chimioprophylaxie = indispensable

Amino-8-quinoléines pour la prévention du paludisme: quand? comment?

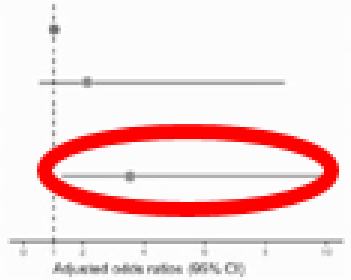
Impact of Chemoprophylaxis on *Plasmodium vivax* and *Plasmodium ovale* Infection Among Civilian Travelers: A Nested Case-Control Study With a Counterfactual Approach on 862 Patients

- 247 *P vivax* (30% sous chimioprophylaxie)
- 615 *P ovale* (47% sous chimioprophylaxie)
- Paludismes graves: 15



Clin Infect Dis. 2022

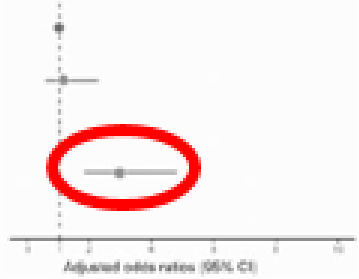
A



P. vivax cases, N=195

	n	Delay between return and onset of symptoms, median (IQR), d	Univariable analysis OR [95% CI]	*P* value	Multivariable analysis aOR* [95% CI]	*P* value
No chemoprophylaxis	137	12 [2–123]	1 (ref)		1 (ref)	
Atovaquone-proguanil	14	38 [28–77]	1.40 [0.49–4.01]	.5	2.14 [0.53–8.62]	.3
Other prophylaxis (doxycycline, mefloquine, chloroquine, chloroquine-proguanil)	44	54 [15–134]	1.97 [1.02–3.83]	.04	3.54 [1.27–9.86]	.02

B



P. ovale cases, N=478

	n	Delay between return and onset of symptoms, median (IQR), d	Univariable analysis OR [95% CI]	*P* value	Multivariable analysis aOR* [95% CI]	*P* value
No chemoprophylaxis	245	15 [3–76]	1 (ref)		1 (ref)	
Atovaquone-proguanil	60	45 [21–86]	1.22 [0.69–2.18]	.5	1.13 [0.55–2.29]	.7
Other prophylaxis (doxycycline, mefloquine, chloroquine, chloroquine-proguanil)	173	79 [24–170]	3.12 [2.10–4.64]	<.001	2.98 [1.85–4.80]	<.001

Pas encore de chimioprophylaxie efficace sur les cryptozoïtes!

Clin Infect Dis. 2022

JAMA | Review

Diagnosis, Treatment, and Prevention of Malaria in the US
A Review

Johanna P. Daily, MD, MS; Aurelia Minuti, MLS; Nazia Khan, MD, MSc, DTMH

Table 4. Malaria Chemoprophylaxis by Dosing Frequency

Drug	During travel		Pretravel	Posttravel	Adverse events (frequency, %)
	Daily	Weekly			
Atovaquone/proguanil (250 mg/100 mg)	X		Daily for 1-2 d before travel	Daily, 7 d	Nausea/vomiting (12)
Doxycycline (100 mg)	X		Daily, 1-2 d	Daily, 30 d	Esophageal ulcers (<1), sunburn (>10)
Primaquine (30-mg base)[a,b]	X		Daily, 1-2 d	Daily, 7 d	G6PD deficiency-associated anemia
Chloroquine (300-mg base)		X	Weekly, 1-2 wk	Weekly, 4 wk	Nausea/vomiting
Mefloquine (228-mg base)		X	Weekly, 1-2 wk	Weekly, 4 wk	Neuropsychiatric (14)
Tafenoquine (200 mg)[c,d]		X	Daily, 3 d	Weekly, 7 d	G6PD deficiency-associated anemia

Long-term safety of the tafenoquine antimalarial chemoprophylaxis regimen: A 12-month, randomized, double-blind, placebo-controlled trial

- Volontaires sains USA/Australie

Characteristic	Tafenoquine (N = 301)	Placebo (N = 298)	Total (N = 599)
Age (years)			
Mean	31.1	31.6	31.3
SD	11.0	10.7	10.9
Median	27.0	29.0	28.0
Range	(18.0–55.0)	(18.0–55.0)	(18.0–55.0)
Gender			
Male	111 (36.88%)	116 (38.93%)	227 (37.90%)
Female	190 (63.12%)	182 (61.07%)	372 (62.10%)

Non-inclusions: déficits en G6PD et grossesse

Travel Medicine and Infectious Disease 45 (2022) 102211

Long-term safety of the tafenoquine antimalarial chemoprophylaxis regimen: A 12-month, randomized, double-blind, placebo-controlled trial

- Volontaires sains USA/Australie (300/300)
- Schéma posologique prophylactique

- Suivi M1, M3, M6, M12 ; suivi thérapeutique pharmacologique

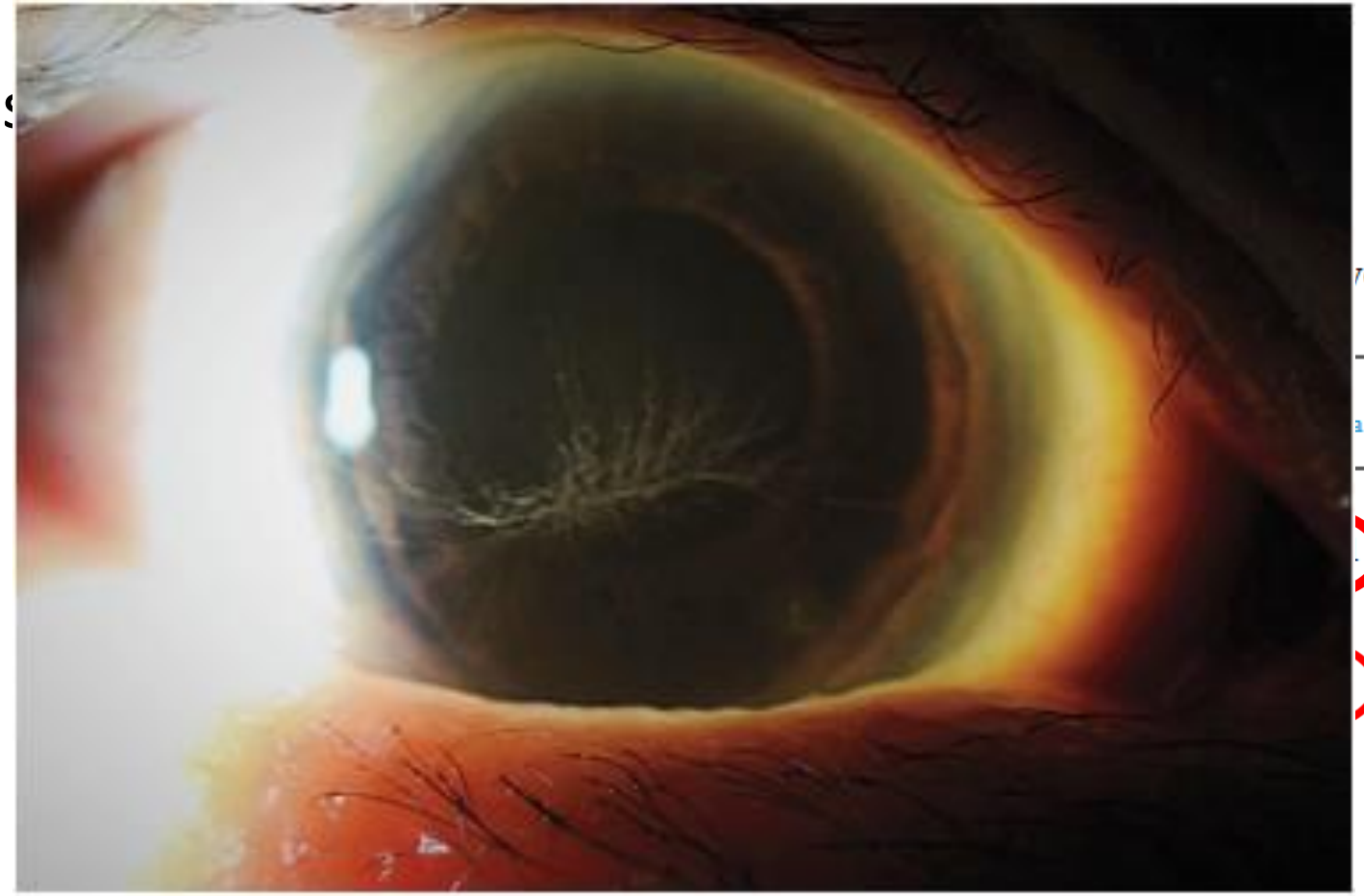
- 15% d'abandon/perdus de vue ; pour EI: 3,7% *vs* 1,7%

- PP: 253 placebo/247 tafénoquine

Travel Medicine and Infectious Disease 45 (2022) 102211

Long-term safety of the tafenoquine antimalarial chemoprophylaxis regimen: A 12-month, randomized, double-blind, placebo-controlled trial

Plus fréquents



N Engl J Med 2015; 372:1656

- Europe

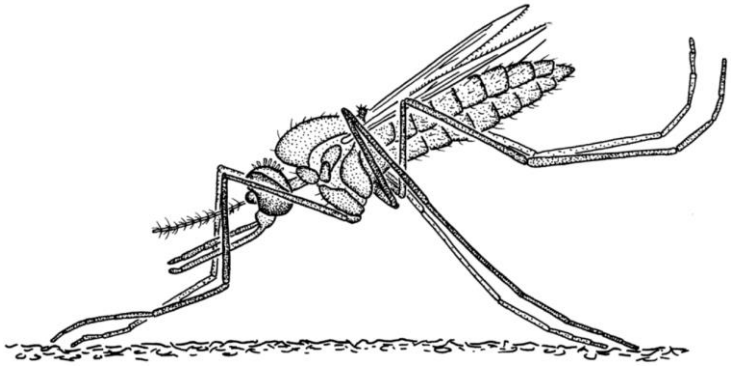
Tafenoquine for malaria chemoprophylaxis – Status quo 2022

Travel Medicine and Infectious Disease 46 (2022) 102268

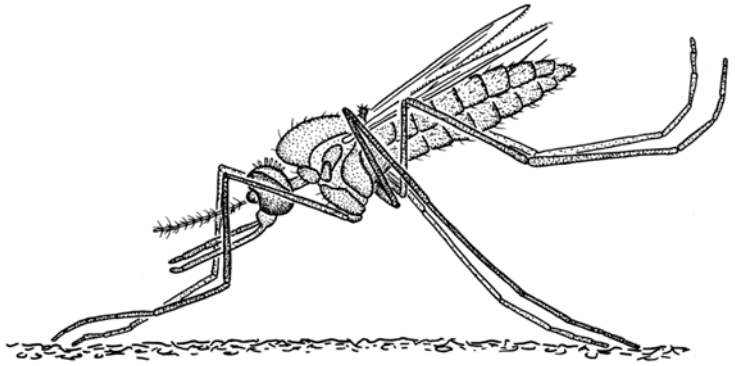
L’immunisation (passive/active) a le vent en poupe

Safety, tolerability, and *Plasmodium falciparum* transmission-reducing activity of monoclonal antibody TB31F: a single-centre, open-label, first-in-human, dose-escalation, phase 1 trial in healthy malaria-naive adults

- Ac murins humanisés anti-protéine Pfs48/45
- Demi-vie d'élimination de 32 jours

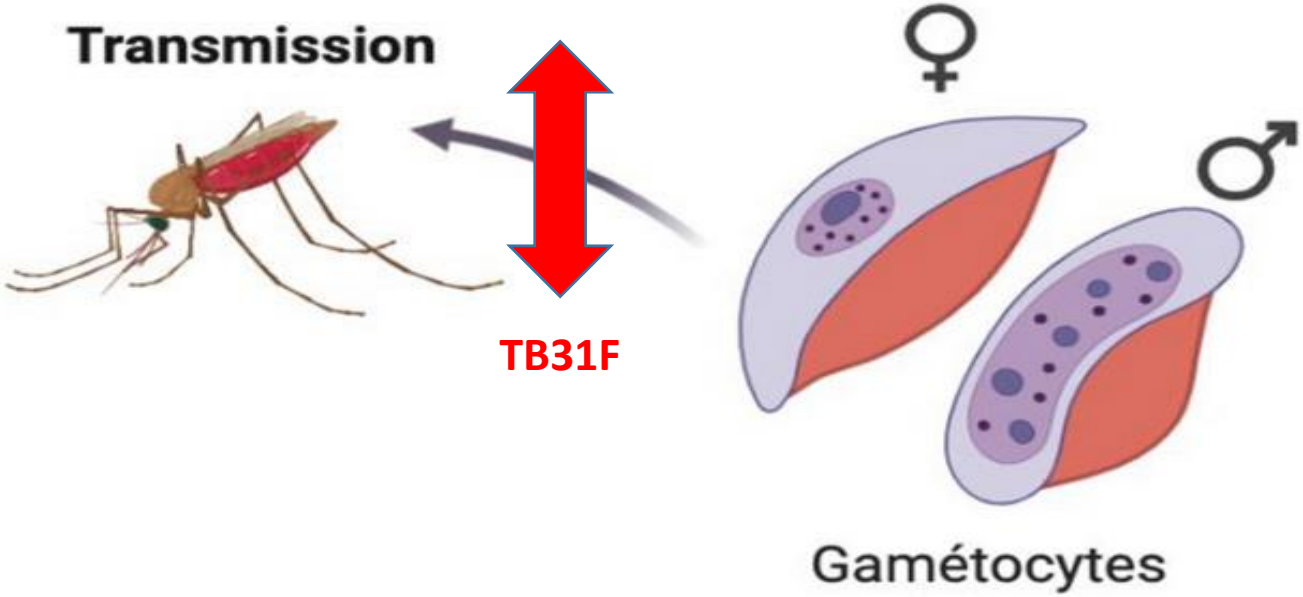


Gamétocytes en culture
+ sérum TB31F



Gamétocytes en culture
+ sérum contrôle

Lancet Infect Dis 2022



- TB31F inhibe fortement (> 80%) l'infectivité chez les moustiques
- Protection jusqu'à 84 jours après une injection de 10 mg/kg
- Intérêt en prévention pendant la saison de haute transmission?

Lancet Infect Dis 2022

Low-Dose Subcutaneous or Intravenous Monoclonal Antibody to Prevent Malaria

- Après le CIS43LS (Ac monoclonal anti-sporozoïtes), **L9LS**
- Voie intra-veineuse (1 mg/kg, 5 mg/kg et 20 mg/kg)
- Voie sous-cutanée (5mg/kg)
- Inoculation expérimentale (vectorielle en laboratoire) de paludisme 2 à 6 semaines chez 23 des 27 participants
- Tolérance et sécurité

N Engl J Med 2022;387:397-407.

Low-Dose Subcutaneous or Intravenous Monoclonal Antibody to Prevent Malaria

- Effets indésirables modérés
- Plus d'effets systémiques après inoculation SC ?

- Demi-vie d'élimination: 56 jours

- Protection partielle: 1 mg/kg IV (4/5) et 5 mg/kg SC (4/5)
- Protection totale: 5 mg/kg (3/3) et 20 mg/kg IV (4/4)
- Protection nulle: contrôles (0/6)

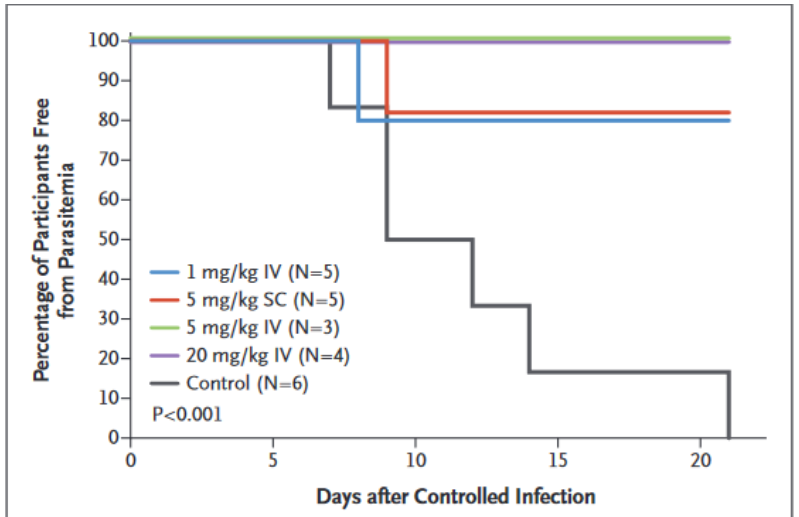
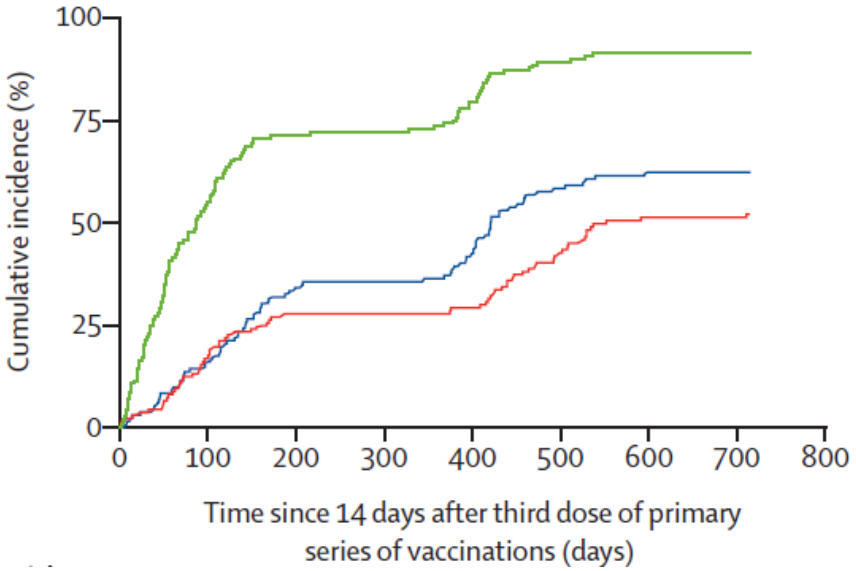


Figure 5. Parasitemia after Controlled Human Malaria Infection.
A Kaplan–Meier analysis shows the time to blood-stage parasitemia as measured by polymerase-chain-reaction analysis. Participants were monitored daily starting on day 7 after controlled human malaria infection through day 17, with a final test performed on day 21. A primary efficacy analysis performed with the use of a two-sided Barnard test comparing parasitemia among the participants who received L9LS with that among the control participants yielded a P value of less than 0.001.

N Engl J Med 2022;387:397-407.

Efficacy and immunogenicity of R21/Matrix-M vaccine against clinical malaria after 2 years' follow-up in children in Burkina Faso: a phase 1/2b randomised controlled trial



From 14 days to 24 months following primary series of vaccinations					
Group 1					
Primary case definition	82/132 (62%)	66% (55–74)	<0·0001	66% (55–74)	<0·0001
Secondary case definition	89/132 (67%)	67% (56–75)	<0·0001	67% (56–75)	<0·0001
Group 2					
Primary case definition	70/137 (51%)	75% (66–81)	<0·0001	75% (66–81)	<0·0001
Secondary case definition	81/137 (59%)	75% (67–81)	<0·0001	75% (67–81)	<0·0001
Group 3 (control group)					
Primary case definition	128/140 (91%)	..	..	..	..
Secondary case definition	131/140 (94%)	..	..	..	..

Phase 3
4800 enfants
5 sites d'Afrique de l'Est et de l'Ouest

- Enfants de 5 à 17 mois
- Taux d'efficacité ≥ 75% (Matrix 50 µg), y compris pour les infections multiples
- Pas plus d'effet indésirable grave qu'avec le groupe contrôle

Lancet Infect Dis 2022

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

MALARIA

A genetically engineered *Plasmodium falciparum* parasite vaccine provides protection from controlled human malaria infection

1) immunisation de volontaires avec la souche vaccinale (PfGAP3KO) par inoculation vectorielle

2) infection expérimentale des volontaires

7 des 14 vaccinés sont protégés

voie ouverte pour un vaccin vivant atténué par voie injectable ?

Protéger le couple mère-enfant …
… dès le premier trimestre de grossesse

Malaria in the First Trimester of Pregnancy and Fetal Growth: Results from a Beninese Preconceptional Cohort

- 1214 femmes suivies pendant 2 ans ; suivi mensuel

- 411 grossesses
- 323 avec échographie précoce
- 218 femmes suivies intégralement (paludisme et croissance fœtale)

    - 109 infections palustres chez 86 femmes
      45 / 35 / 29

Pas d'impact sur la croissance fœtale, du paludisme au cours du 1er trimestre

Le paludisme grave encore et toujours …

Non-traumatic coma in young children in Benin: are viral and bacterial infections gaining ground on cerebral malaria?

- 84 comas non traumatiques , 2018, Cotonou et Abomey-Calavi
  - 70 paludismes graves
  - 8 co-infections (2 bactériémies, 1 méningite purulente, 2 rougeoles, 1 West-Nile, 1 adénovirus, 1 HHV6)
  - 6 comas non palustres (1 bactériémie, 1 dengue, 1 rougeole, 3 indéterminés)
- Occasions manquées
  - 27/78 (34 %) ont reçu un antipaludique
  - 21/27 : non CTA (ACT)

Table 4 Factors predictive of death in the multivariate analysis

Variable[a]	*OR*	95% *CI*	*P*-value
Hyperlactatemia (lactate > 5 µmol/L)	8.6	2.03–36.1	0.004
Jaundice or increased bilirubin (> 50 µmol/L)	5.1	1.49–17.30	0.009
Antibiotics before admission[b]	0.1	0.02 –0.85	0.03
Yellow fever vaccination	0.2	0.05 – 0.79	0.02

OR odds ratio, *CI* confidence interval

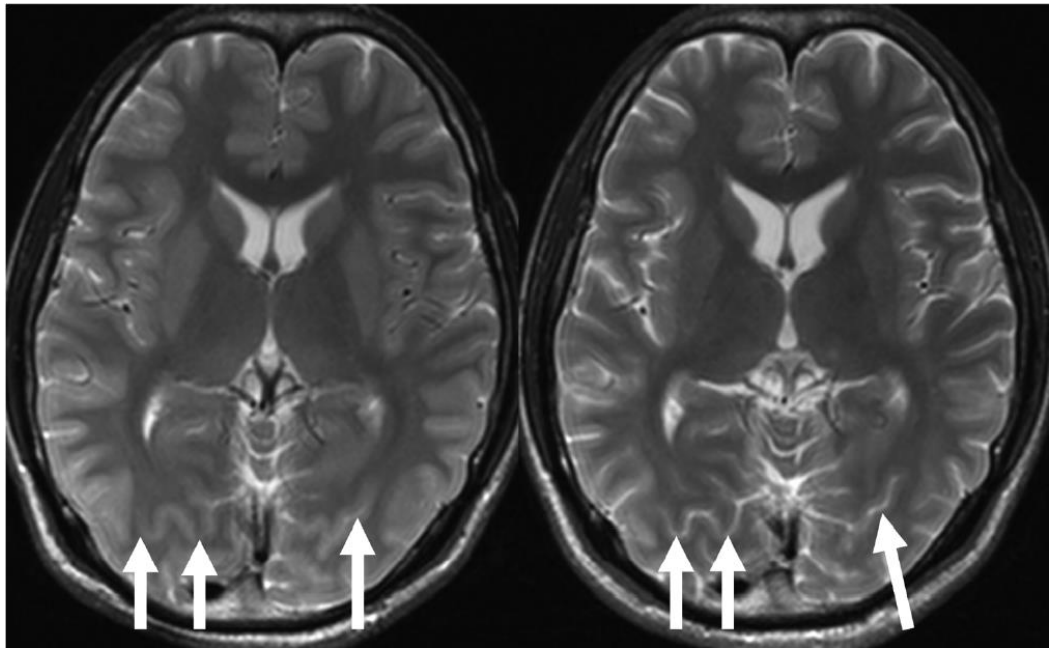
[a] Adjusted by center

[b] Between disease onset and admission

Infectious Diseases of Poverty (2022) 11:29

Evidence of Brain Alterations in Noncerebral Falciparum Malaria

- Arguments d'imagerie
  - Œdème
  - Calcul du coefficient de diffusion apparent (CDA)

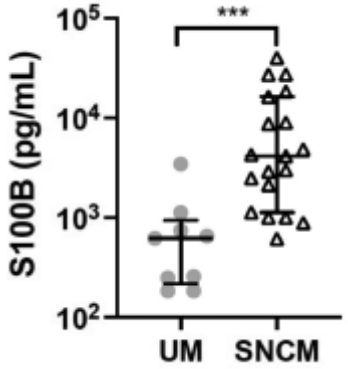


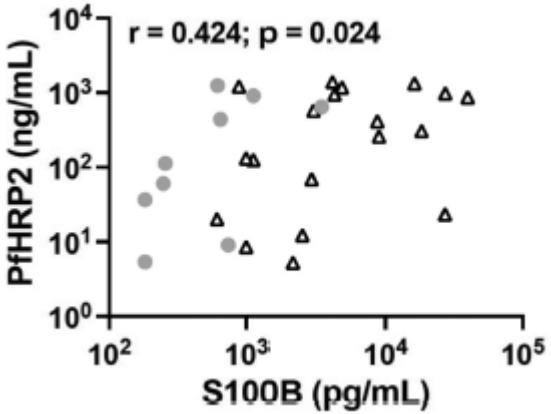
- Paludisme non compliqué: 20
- Paludisme grave non neurologique: 21
- Contrôles: 5

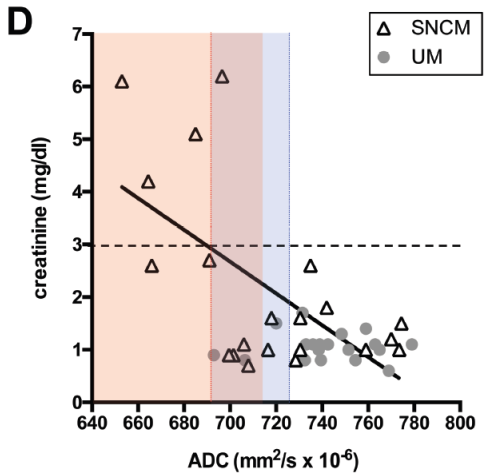
  - Paludisme grave sans signe neurologique: oedeme cytotoxique (CDA bas)
  - Paludisme non compliqué: oedeme vasogénique (CDA élevé)

Evidence of Brain Alterations in Noncerebral Falciparum Malaria

- Arguments biologiques



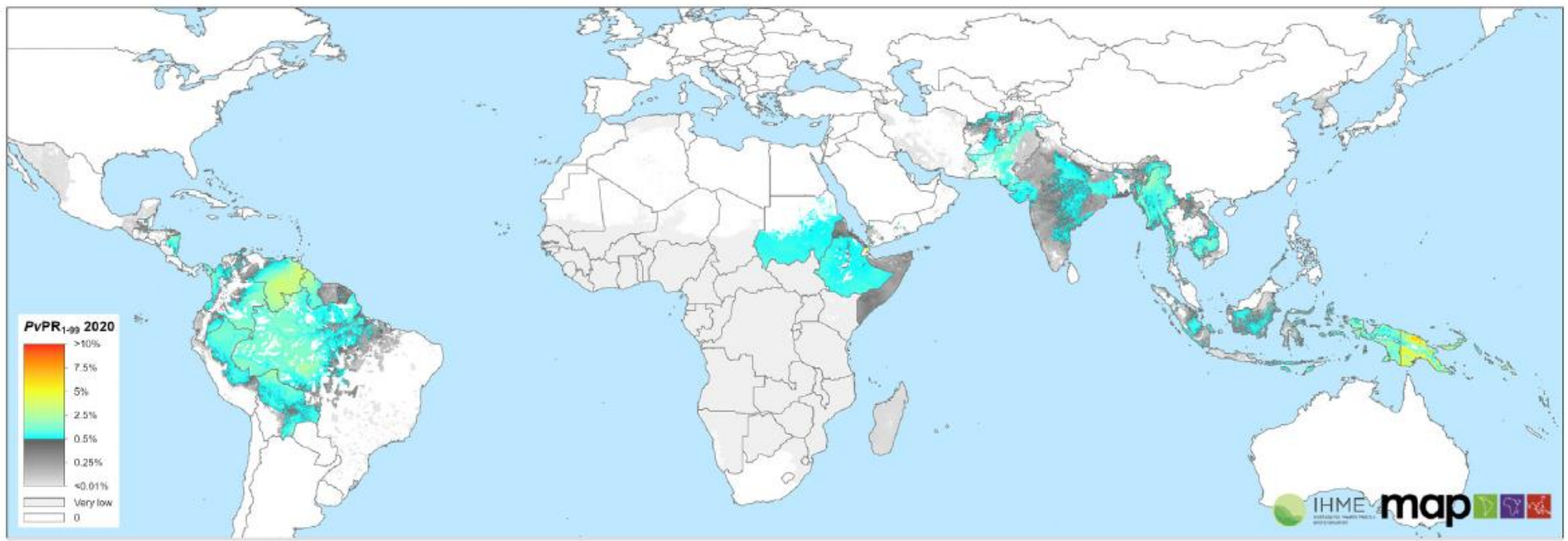




Vivax en Afrique

African *Plasmodium vivax* malaria improbably rare or benign

J. Kevin Baird [1,2,*]



Trends in Parasitology

Figure 1. Global distribution of *Plasmodium vivax* prevalence during 2020. Map modeled using reported patent infections, with permission of the Malaria Atlas Project (https://malariaatlas.org/trends/region/MAP/GLOBAL).

Biomasse extra-vasculaire
Vivax > *falciparum*

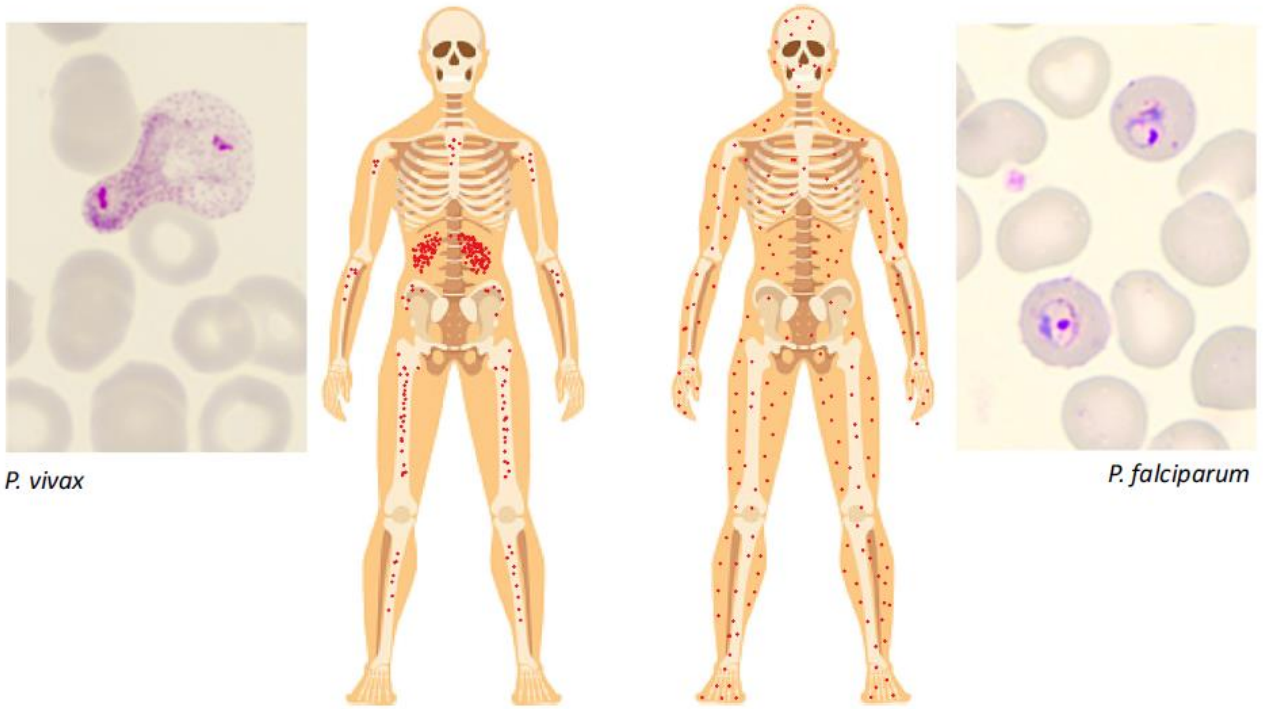


Figure 2. Dominant anatomic sites of schizogony in *Plasmodium vivax* versus *Plasmodium falciparum*.
For a Figure360 author presentation of Figure 2, see the figure legend at https://doi.org/10.1016/j.pt.2022.05.006.
Trophozoites of *P. vivax* and *P. falciparum* in Giemsa-stained thin blood films taken from acutely ill residents of Sumba in southeastern Indonesia, illustrating the conspicuous deformability of red blood cells (RBCs) infected by *P. vivax* and the motility needed to do so versus the absence of both in *P. falciparum* (specimens courtesy of Claus Bogh of the Sumba Foundation at Sumba, Indonesia, and photomicrographs by Lenny Ekawati at the Eijkman-Oxford Clinical Research Unit, Jakarta, Indonesia; reprinted with permission). The human figures illustrate hypothesized dominating anatomic sites of blood schizogony in humans infected by *P. vivax* or *P. falciparum* . In *P. vivax*, these are in the accessible extravascular spaces of bone marrow and those of the spleen and liver, where extramedullary erythropoiesis may occur, providing the $CD71^+$ immature reticulocytes required for *P. vivax* propagation. The scarcity of those host cells in peripheral circulation limits capacity for parasitemia. In *P. falciparum*, promiscuous invasion of any RBC makes that entire organ system hospitable to propagation (and fulminant parasitemia).

Trends in Parasitology, August 2022, Vol. 38, No. 8

C’est la fin …

NIVAQUINE 100 mg cp séc — Sanofi-Aventis France

Suite à des difficultés de fabrication, la commercialisation de Nivaquine 100 mg comprimé sécable sera arrêtée à compter de septembre 2022.
Des alternatives thérapeutiques sont disponibles dans le traitement préventif ou curatif du paludisme, notamment pour la population pédiatrique.
En savoir plus.

Publié le 25/07/2022

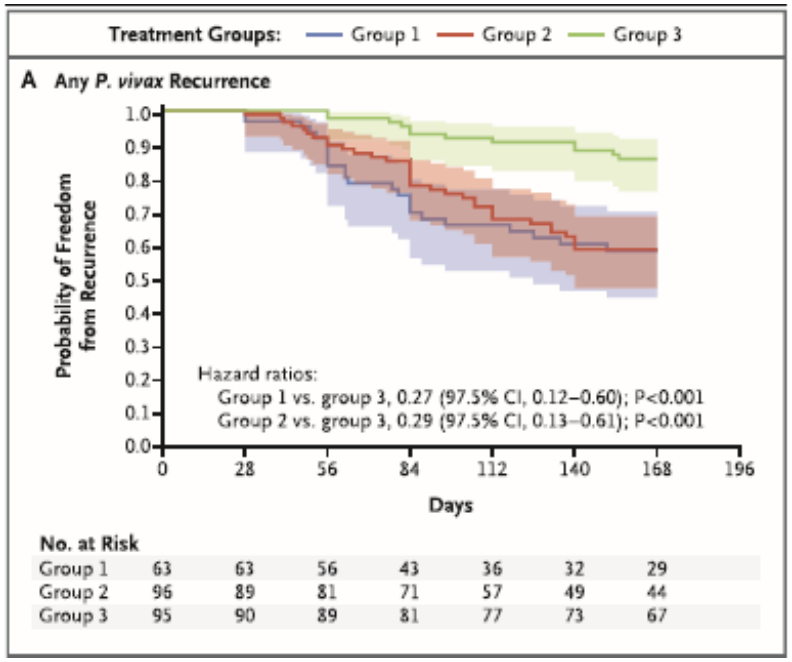
Effectiveness of pyronaridine-artesunate against *Plasmodium malariae*, *Plasmodium ovale* spp, and mixed-*Plasmodium* infections: a post-hoc analysis of the CANTAM-Pyramax trial

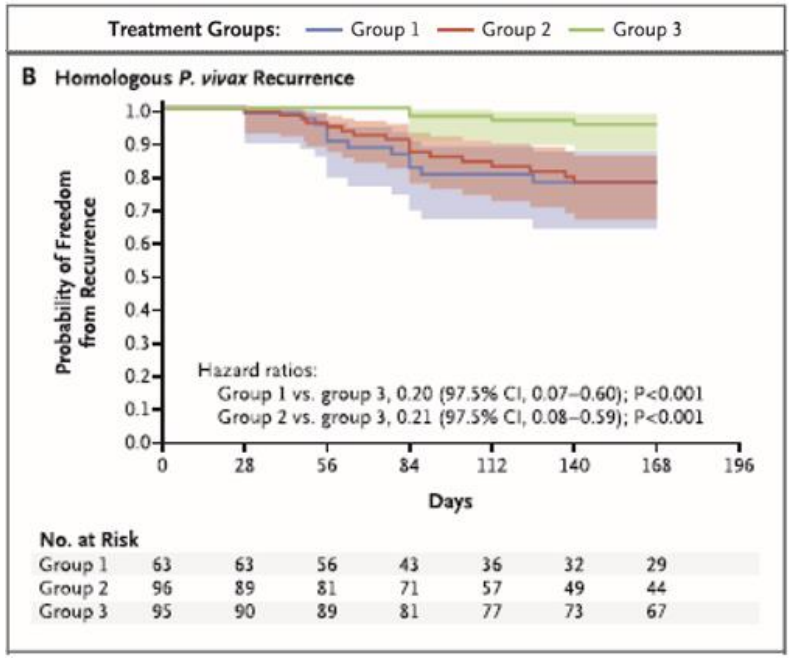
- 192 paludismes *non falciparum* ; Gabon et RDC
- Taux d'efficacité>95% à J28
  - *P malariae* (128)
  - *P ovale curtisi* et *wallikeri* (74)

Lancet Microbe 2022; 3: e598–605

Primaquine – Vivax au Brésil

- 0,5 mg/kg/j ; 7 j *vs* 14 j





Efficacité 7 jours: 78%

Efficacité 14 jours: 95%

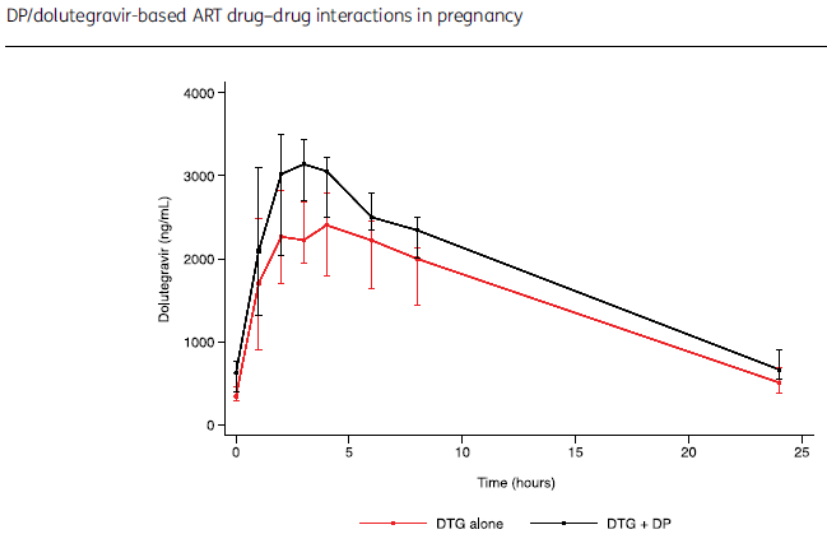
N Engl J Med 2022;386:1244-53.
DOI: 10.1056/NEJMoa2104226

22 juillet 2019

L'OMS recommande le dolutégravir comme option thérapeutique à privilégier contre le VIH dans toutes les populations

Effect of dihydroartemisinin/piperaquine for malaria intermittent preventive treatment on dolutegravir exposure in pregnant women living with HIV

- Amodiaquine-artésunate: Risque de sous dosage du dolutégravir en administration concomitante
- Quid de DHA-pipéraquine?
- 12 femmes enceintes (2ème et 3ème trimestre)
- Augmentation de l'AUC et de C Max de 30% environ
- Bonne tolérance clinique



J Antimicrob Chemother 2022; **77**: 1733–1737