



## Letter

## In response to the letter to the editor by Dondorp et al. RE: Reuling et al., 2018 ‘liver injury in uncomplicated malaria is an overlooked phenomenon: An observational study’



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Dondorp et al. highlight that the incidence of liver function test (LFT) abnormalities (> 5.0x the upper limit of normal (ULN)) in SE-Asian malaria patients after artemisinin combination therapies (ACTs) is roughly three times more than observed in Controlled Human Malaria Infection (CHMI) studies in malaria naïve-Dutch volunteers and uncomplicated falciparum malaria in returning travelers [1,2]. This remarkable difference indeed requires further consideration.

The difference may relate to study design with differences in sample collections in particular. In Reuling et al., we show that numbers and moment of sampling may clearly impact on the observed incidence of severity of LFT abnormalities [2]. The peak of LFT abnormalities often occur during a very brief period (day 1–3 post-treatment), which therefore may be missed in van der Pluijm et al.'s study [1]. This may, however, not be a completely satisfactory explanation as other factors may come into play.

Dondorp et al. suggest that observed differences may relate to the use of laboratory-adapted strains in the CHMI model. We consider this possibility less likely, since geographically/genetically distinct strains- (NF54, 3D7, NF135, and NF166) have been used in our CHMI's conducted between 2001 and 2016 showing similar results. Furthermore, as shown in Woodford et al. [3], the LFT abnormalities are not batch, or site-specific, neither limited to *Plasmodium falciparum*, but also occurring in *Plasmodium vivax* challenges.

A more plausible explanation, in our opinion, may be the degree of pre-existing malaria immunity. This is clearly different in the two study populations ie, malaria naïve-Dutch versus

malaria endemic SE-Asian. In Reuling et al. we do suggest that liver injury is caused by systemic inflammation by associating pro-inflammatory markers to LFT abnormalities [2]. Consequently, pre-existing immune responses may mitigate inflammatory responses to the challenge infection and subsequently reduce liver cell damage. This hypothesis is supported by a more recent CHMI conducted in The Gambia [4], a setting with low entomological inoculation rates, where pre-existing immune status was defined by serologic markers. Just 2 out of 17 (11.8%) Gambian participants that were challenged and became thick smear positive, showed only mild LFT abnormalities (elevated gamma glutamyl transpeptidase ( $\gamma$ GT) and aspartate aminotransferase (AST)). Furthermore, Spence et al. [5] show that when CHMI volunteers were infected three times over a course of 12 months, no liver damage was observed after the third infection.

The insightful comment by Dondorp et al. highlights that safety outcome in clinical trials with new anti-malarials may at least also depend on the immune status of the study population resulting in a ‘green or red flag’ rather than a ‘false flag’.

### Declaration of Competing Interest

The authors have no competing interests.

### CRedit authorship contribution statement

**Isaie J. Reuling:** Writing – review & editing. **Gerdie M. de Jong:** Writing – review & editing. **Perry J.J. van Genderen:** Writing – review & editing. **Robert W. Sauerwein:** Writing – review & editing.

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