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Dear Editor

The retrospective analysis by Gutman and colleagues[1] provides a useful contribution to the knowledge of Atovaquone-proguanil (AP) use during pregnancy.

The combination regimen has been licensed for nearly 20 years as a chemoprophylaxis agent. The combination came off patent in 2013 and is now widely available as a generic drug. To date, no large prospective controlled safety studies in pregnant women have been published. It is unlikely such studies will become available in the near future, in part because the combination is not used in malaria endemic countries because of its high cost, to provide a more conclusive picture of AP 's safety during pregnancy; a situation which the authors recognise. To interpret pregnancy safety outcomes, we have to rely on less than ideal smaller studies and pregnancy registry analysis. We also have some supportive safety insight from experience of the constituent drug's use in pregnant women prior to their combination.

The authors compare pregnancy outcomes of military women, some using AP (n=50) and other drugs , to a much larger control group. They find a non-

statistically significant increase in the risk of fetal loss and a composite adverse live birth outcome indicator. The Hazard ratio for any AP exposure is 1.5 with 95% CI (0.90, 2.67) and any live birth outcome OR of 1.55 95% CI (0.71, 3.71). The significance of these are both greater than 5%. The authors accurately describe the statistical reliability in their discussion, as lacking in power to detect associations between drug and adverse events, and that larger numbers of exposed pregnancies are necessary to understand AP exposure to pregnancy outcomes.

It was therefore surprising to read their conclusion from the above findings that AP should not be used for prophylaxis, or treatment, in pregnant women and that it would be difficult to recommend a randomised controlled trial with AP, based on these findings.

The authors have previously published on AP outcomes in pregnancy, in which they have concluded that "*rates of adverse events after AP exposure during pregnancy are not higher than the expected rates in similar populations,"*[2] and "*no specific signal to suggest a teratogenic effect of AP, AP data during pregnancy*"[3] and there is "*limited evidence of the safety of AP in pregnancy*" [4]. Similar findings have been reported in the largest analysis of AP in pregnancy by a Danish registry study of AP safety in early pregnancy.[5]

We feel it is unreasonable to restrict an effective and tolerable drug from one of the most vulnerable groups of travellers. The authors make a recommendation based on low numbers and no statistical validity which is against the majority of published evidence. The decision to prescribe should be left to the individual professional prescriber and not the risk threshold of study authors.

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