Adherence to antimalarial treatments in the real world – does it really matter?

Medicines for Malaria Venture's Adam Aspinall discusses patient adherence to antimalarials and the pipeline of future medicines set to improve it

Adherence, compliance, concordance – whichever term you prefer, all refer to the extent to which patients take their medication as prescribed.[1,2] The three key elements involve taking a medicine at the right dose, the correct dosing frequency and for the recommended treatment duration.[3] Failure to take medicines as recommended has negative consequences; for some therapeutic areas, such as the treatment of musculo-skeletal disorders with non-steroidal anti-inflammatory drugs, poor adherence may 'only' result in inadequate symptom control. For diseases such as uncomplicated malaria, the consequences can be far more serious; sub-optimal adherence has been associated with treatment failure, severe malaria and death.[1,3,4] For example, Siddiqui et al. reported patients returning to a Médecins Sans Frontières clinic in the Democratic Republic of the Congo[4] with severe malaria despite having been prescribed artemisinin-based combination therapy (ACT) treatment. While it was not known if this was a result of treatment failure or re-infection, the study also showed that ACT adherence in the setting was inadequate. Of particular concern is the potential for the development of drug resistance, which is more likely to emerge in patients with the lower drug levels that may result from poor adherence.[5]

It might be logical to assume that, since malaria is a potentially fatal condition, patients would have a strong incentive to take their medication correctly and to finish the prescribed course. However, the latest literature suggests a rather different story, and since malaria symptoms usually improve rapidly with ACTs there is a strong temptation not to complete the 3-day course of treatment and to keep leftover medicines for future malaria episodes.

In 2013, Medicines for Malaria Venture (MMV) conducted market research with patients, healthcare providers and policymakers in six African countries, designed to inform the development programme for a single exposure cure for uncomplicated malaria. While the research was primarily focused on formulation preferences, during the conversation participants were also asked about how often they completed the full 3-day course of ACT treatment. Astonishingly, not one of the more than 100 participants said they routinely completed the full treatment course. Even a Director of Public Health confided that: 'I know I should, of course, but with ACTs I feel better so quickly that, to be honest, I usually only take the first two or three doses'. Similar responses were heard repeatedly from patients in all six countries: 'The drugs work fast. Once the fever goes away, I don't take them anymore. Kids probably get all the doses, but not adults'. Unfortunately, however, even this assumption that children are generally correctly dosed may not be accurate: a 2015 meta-analysis by Yakasai et al.[6] found that poor ACT adherence was mainly related to the last two doses of treatment, but also confirmed generally poor adherence in children under 5 years, possibly due to the lack of appropriate paediatric formulations.

So to what extent is adherence lacking in reality – and does it really matter? In sub-Saharan Africa, ACTs are still highly effective and there is no firm evidence as yet of artemisinin-resistant malaria on the continent. At the same time, there is little to suggest that widespread sub-optimal adherence is undermining malaria case management in the region.

A quick look at the literature reveals no simple answer. At first glance, there appears to be a discrepancy between studies and anecdotal field feedback, particularly when looking at earlier publications which tend to show antimalarial adherence levels of around 60%.[7–11] As ACT use has increased over the past 10 years, the number of studies investigating adherence has grown proportionately. However, this proliferation of data is complicated by the many different methodologies and definitions used, meaning that it is difficult to compare studies on a like-for-like basis.[3] This was highlighted by Bruxvoort et al. in their 2015 systematic review of 55 studies,[3] which found a remarkably wide range of reported adherence across various studies, and further reinforced by another recent systematic review[12] that reported ACT adherence levels from less than 30% in Kenya to 100% in Malawi.

It seems clear, therefore, that incomplete adherence is both common and widespread. While there is still some debate about which aspects (such as correct timing of dosing, completing the course or even taking with fat-containing food) are most important,[3] all measures that improve adherence – whether better education and training, more child-friendly medications, or new drugs with less frequent dosing – have an important role to play in addressing the current situation.

Since antimalarial adherence has been reported to be inversely proportional to the length of therapy and dosing frequency,[14] this would imply that antimalarials which offer less-frequent and even single-exposure dosing should facilitate a significant improvement. Apart from artemether-lumefantrine, which is administered twice daily for 3 days, the other four ACTs recommended by the World Health Organization[13] already offer once-daily dosing for 3 days. Looking ahead, the majority of next-generation antimalarials currently in development

Adam Aspinall is Director, Product Strategy & Management, at Medicines for Malaria Venture (MMV).

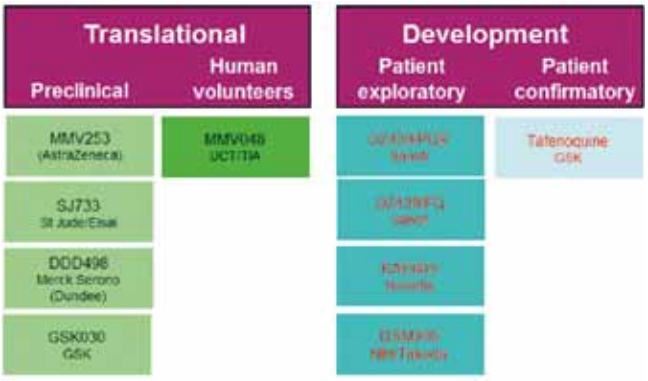


Figure 1: Potential single exposure candidates in the translational and development phases of MMV's drug development portfolio

for uncomplicated *P. falciparum* malaria have single-dose potential intended for administration as Directly-Observed Therapy (DOT). In addition, tafenoquine, a single-dose treatment for the liver-stage of *P. vivax*, which could form part of a radical cure for malaria, is being developed by GSK and MMV as an alternative to the current 14-day treatment regimen with primaquine.

MMV's drug development pipeline currently includes a number of candidates with the potential to be single-exposure cures in combination with partner drugs. This aligns with MMV's strong focus on developing next-generation Single Exposure Radical Cure and Prophylaxis (SERCaP) and Single Exposure Chemoprotection (SEC)[14] compounds to provide single dose curative and chemoprevention treatments.

Of the later-stage combinations, the most advanced is OZ439 (artefenomel) + piperaquine, currently in a late-stage phase IIb study, while OZ439 + ferroquine has recently entered phase IIb. Other promising compounds are following closely behind, and within the coming years malaria patients should have new treatment options delivered via a simple, single dose. The long-term vision is that this will result in less treatment failures, fewer episodes of severe malaria, lower costs for re-treatment and unnecessary hospital admissions, and ultimately fewer deaths.

However, dosing frequency and treatment duration are not the only factors which influence whether and how patients take their antimalarials. Adherence appears to be significantly poorer in children under 5 years, possibly due to the unpalatable taste of some antimalarials and lack of child-friendly formulations.[5] This is of particular concern since the vast majority of deaths from malaria are in this age group, and the likelihood of developing resistant parasites is greater than in adults due to their higher parasite biomass.[15] As a result, MMV has prioritised the development of child-friendly formulations, designed to meet the very specific needs of this patient group. Indeed, the first medicine to emerge from MMV's pipeline was Coartem® *Dispersible*, co-developed with Novartis; last year, this cherry-flavoured, child-friendly treatment surpassed the landmark of 250 million courses distributed since its launch in 2009. Looking forward, OZ439-combination treatments will be developed as orange-flavoured granules – with the flavouring informed by field research on palatability in paediatric patients.

In summary, given the ample evidence of incomplete adherence, it seems certain that there is significant room for improvement in practice. The serious long-term consequences of poor adherence to antimalarial treatment cannot be overstated. This applies not only at the individual patient level, but also at the global level, where protecting ACTs from the emergence of resistance is paramount. Education and training – both of healthcare recipients and providers – remain crucial. Community health workers, public health officials, pharmacists and drug manufacturers all have important roles to play through education, monitoring, and the development and appropriate use of clear packaging and patient information. Innovative solutions such as SMS reminders targeted at patients and providers are not yet widespread but are currently being field tested.

Finally, the good news is that the pipeline for antimalarial drugs has never been stronger. As of the end of the first quarter of 2015, there are more than 30 drug candidates in the translational and developmental phases of the global antimalarial portfolio. While not all these candidates will survive the rigorous clinical development process, the next decade is likely to see the introduction of a number of single-exposure antimalarials, representing a significant leap forward from 3-day treatment regimens and a new era in malaria treatment. The future looks bright indeed.

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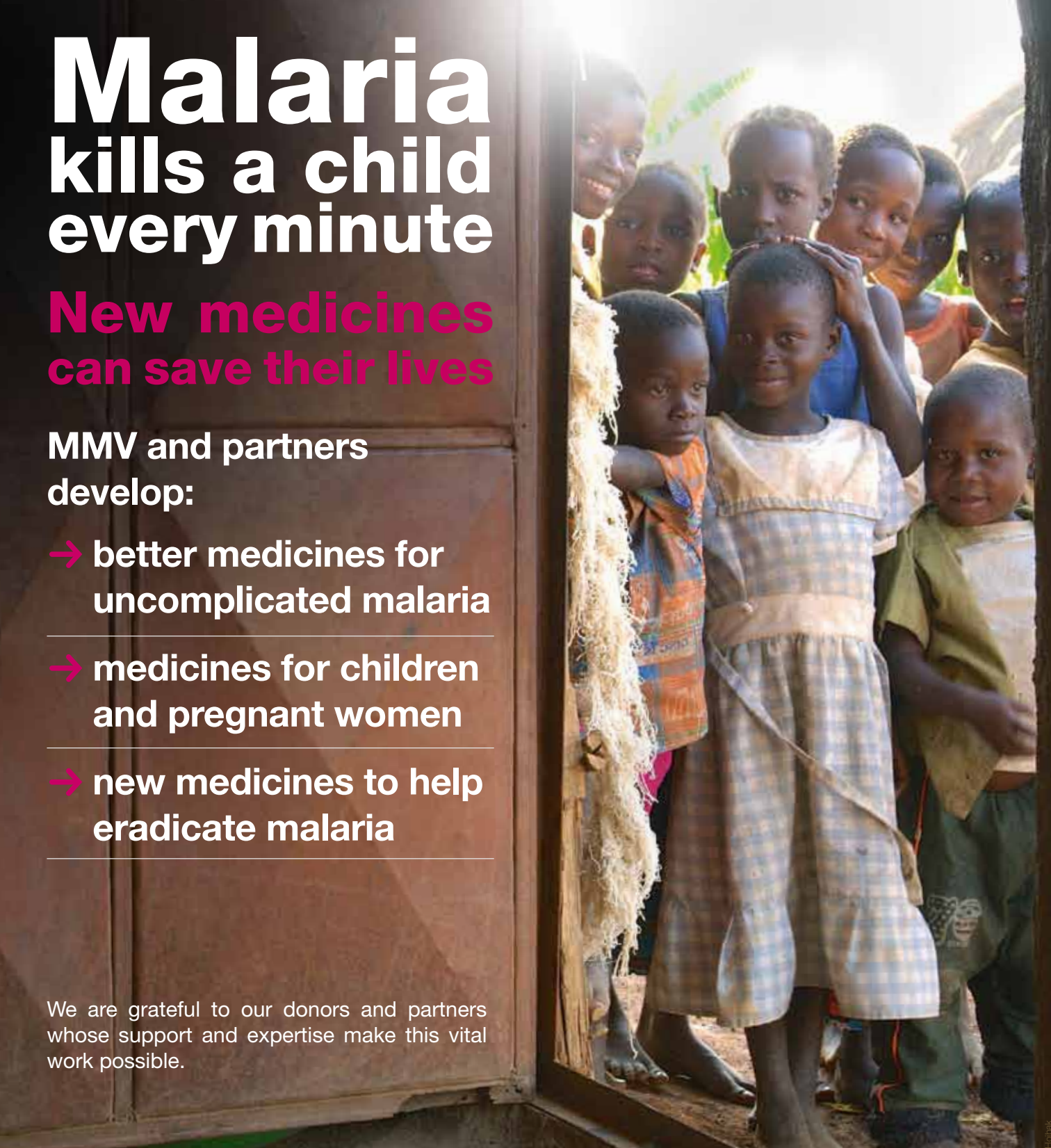


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