

# Compliance and adherence to primaquine treatment in Myanmar

## a brief of available evidence

### Background

This brief aims to draw together currently available evidence on health worker compliance and patient adherence to primaquine radical cure.

The Myanmar National Malaria Control Program (NMCP) aims to eliminate all species of malaria by 2030 starting with *Plasmodium falciparum* elimination by 2025 and *Plasmodium vivax* elimination by 2030. This requires the country to demonstrate no malaria cases as of 2029 to enter the malaria elimination certification phase and achieve malaria-free status by 2032. As the NMCP progresses toward elimination, the relative burden of *P. vivax* is increasing, accounting for 60 percent of all malaria cases in 2019.<sup>1</sup> *P. vivax* treatment is challenging, primarily because of the dormant liver (hypnozoite) stage, which can awaken and cause new episodes (relapse) of malaria without a further mosquito bite. Patients with dormant *P. vivax* infection represent a human reservoir of infection, which substantially contributes to the disease burden. Radical cure, meaning both treating the blood-stage infection and eliminating hypnozoites from the liver, is essential for successful elimination of this malaria species.

The liver-stage of *P. vivax* is treated using primaquine either for 14 days or for 8 weeks according to the treatment guidelines outlined by the Myanmar Ministry of Health and Sports. World Health Organization guidelines state that, where feasible, health workers should use the Glucose-6-phosphate dehydrogenase (G6PD) status of patients to guide the administration of primaquine, including the length of treatment. A patient with normal G6PD enzyme levels can be given a 14-day treatment course (0.25 mg/kg). However, patients with low G6PD enzyme activity (i.e., G6PD deficient patients) are at risk of haemolysis from primaquine and therefore a primaquine regimen spread over 8 weeks (0.75 mg/kg) with close medical supervision can be considered. However, G6PD diagnostic tests are not currently available within the health system in Myanmar and are not currently mandated in the national guidelines.

Data on primaquine treatment compliance and adherence in Myanmar is fragmented and limited. The outputs of this brief can be used to shape treatment and education packages to improve overall quality of care for *P. vivax* cases and reduce *P. vivax* transmission. A summary of findings is provided in the box below, followed by more detail from literature and reports.

## Myanmar – Compliance and adherence to primaquine

### Summary of findings from literature and reports

*More detail and references are available following this summary*

#### **Health worker compliance to radical cure treatment is variable, and in some cases unsatisfactory.**

Overall, recent data indicates that health worker compliance to, or correct implementation of, national treatment guidelines for *P. vivax* and mixed infections ranges from 70 to 95 percent.

#### **Why?**

- Not knowing patients' G6PD status deters health workers from prescribing primaquine.
- If health workers perceive that patients will not adhere to primaquine treatment, they are less willing to prescribe it.

#### **Patients do not generally adhere to longer treatment regimens.**

More than half of patients are likely to be non-adherent to a 14-day *P. vivax* treatment. Adherence tends to decrease starting at day 3 and this decrease doubles after day 7 of treatment.

#### **Why?**

- Patient recovery and cessation of malaria symptoms after 3-day blood-stage treatment with chloroquine.
- Limited patient understanding of the importance of completing *P. vivax* treatment.
- Patient forgetfulness.
- Gastrointestinal side effects.

#### **What could be done to address health worker compliance and patient adherence?**

- Determine how to increase access to G6PD testing. New point-of-care G6PD tests are becoming available globally and in Myanmar. Determining the feasibility of their use at different levels of the health system is essential. As most *P. vivax* cases now present at community levels, it will be important to determine how Integrated Community Malaria Volunteers (ICMVs) will have access to information on a patient's G6PD status.
- Create clear messages during training on case management to ensure health workers understand the reasons for prescribing primaquine and how they can communicate with patients to increase adherence.
- Improve interpersonal communication of health workers. Health workers need to provide clear explanations to patients on: (1) why they are being prescribed primaquine, (2) the importance of completing the course, (3) identifying a time in the day when patients should take their primaquine medication to avoid gastrointestinal issues, (4) identifying a tracking tool, (5) the potential side effects of primaquine, and (6) what actions to take in case of adverse events. Better

communication tools for health workers tailored to local needs could help facilitate these explanatory conversations with patients.

- Remind patients to complete their course of treatment and monitor for severe adverse events either through directly-observed therapy at health facilities or home visits.
- Train ICMVs, health centers, and referral hospitals on recognizing and referring patients with severe adverse events to increase ICMV and health center confidence in prescribing primaquine.

**What else do we need to know?** This brief is based on limited literature on compliance and adherence to primaquine treatment. More data, and more standardized data, is needed to better understand health worker compliance and patient adherence. Robust evaluation of ongoing implementation activities could improve NMCP decision-making around how to increase compliance and adherence.

## Detailed findings from literature and reports

### How much do health workers currently comply with *P. vivax* treatment algorithms?

- In Ethnic Health Organisation supported areas, 95 percent of patients with mono-infections received the correct drugs in the correct dose and adequate duration appropriate to malaria species, age, and pregnancy status. However, 30 percent of patients with mixed infections were not treated correctly.<sup>2</sup>
- A review of countrywide NMCP statistics by Linn et al. in 2018 found health workers prescribed ‘complete treatment’ for 80.9 percent of patients seen by Village Health Volunteers and 88.2 percent of patients seen by Basic Health Staff.
- In 2018, Linn et al. found that of those eligible for artemisinin-based combination therapy (n = 14,756), chloroquine (n = 6,619), and primaquine (n = 20,375), a total of 14,093 (95.5 percent), 5,209 (92.7 percent), and 17,029 (83.6 percent) received the treatment, respectively.<sup>3,4</sup>
- In 2011, Save the Children found that most service providers (87 percent) fully complied with the national malarial treatment guidelines.<sup>5</sup>

### What factors influence health worker compliance?

#### *Unknown G6PD status:*

- Narrative reports from Ethnic Health Organisations described ICMVs as having concerns about prescribing primaquine to people with unknown G6PD status.<sup>2</sup>
- Health workers interviewed by Han et al. in 2018 explained that they were reluctant to use primaquine for patients when they were unsure of their adherence to treatment rather than any safety concerns or contraindications.<sup>6</sup>

- In another study in Hpapun Township, Karen state, along the Myanmar-Thailand border, which is one of the highest malaria prevalence areas in the country, fear of G6PD deficiency and its complications after prescribing primaquine was a factor in treatment provision.

#### *Familiarity with NMCP national treatment guidelines:*

- In 2016, Lwin et al. reported that 72 percent of health care providers highlighted that understanding the rationale for prescribing primaquine as part of antimalarial treatment empowered health workers to prescribe it. Another 12 percent identified training on national treatment guidelines as a factor that encouraged them to comply with treatment guidelines.<sup>5</sup>
- Health workers' reasons for not prescribing primaquine according to Lwin et al. (in a study undertaken in 2011), were drug contraindications, issues with training or guidance, unknown G6PD status, and concerns about the side effects of primaquine.<sup>5</sup>
- Service providers with a high knowledge score were 2.9 times (95 percent CI 1.04–8.14) more likely to comply with the national treatment guideline ( $p = 0.037$ ).<sup>5</sup>
- Private sector providers are not familiar with national treatment guidelines due to the decreasing number of malaria cases and infrequent experience of treating malaria patients (ACTwatch).<sup>7</sup>

#### *Primaquine supply chain:*

- Primaquine is available in the formal public sector, but availability is lower at community levels. Han et al. found that public sector staff reported an adequate stock of primaquine. At these service delivery points, they did not report any stock-outs of primaquine within the last three months. However, only 75 percent of community health workers reported having primaquine stock (ACTwatch).<sup>7</sup>
- There is a gap in the supply of primaquine in the private sector. Primaquine was unavailable in the retail market, such as general practitioners clinics without connection to nongovernmental organizations or unlicensed drug shops during an ACTwatch study (2017). In this sector, availability of any component of *P. vivax* treatment (chloroquine and/or primaquine) was 56.2 percent.

#### **Do patients adhere to radical cure treatment?**

- More than half of patients are likely to be non-adherent to *P. vivax* treatment (Lwin et al. 2016). Among *P. vivax* and mixed infection patients who had been prescribed primaquine by health staff (14-day regimen), 12 percent were certainly non-adherent (either admitted not talking all medicines or had leftover pills at the interview). A total of 44 percent of patients were probably non-adherent due to reporting incorrect use of prescribed primaquine regimen. Hence the remaining 44 percent were probably adherent to prescribed regimen.<sup>5</sup>
- Adherence likely begins to decrease after day 3 of treatment. Nonadherence can double after day 7 of a 14-day primaquine treatment course. Aung et al. (2015) found that the likely non-adherent rate for a 3-day course of artemether-lumefantrine for *P. falciparum* was 14.3

percent.<sup>8</sup> Further, Takeuchi et al. (2010) found nonadherence doubled in the second week of treatment, even after a study visit to patients on day 7.<sup>9</sup>

### What factors improve patient adherence to treatment?<sup>5</sup>

- Home visits or health facility-based Directly-Observed Therapy in a health facility significantly increased adherence in patients by an odds of 2.28 (95 percent CI 1.06–4.89,  $p = 0.035$ ) and 2.02 (95 percent CI 1.18–3.45,  $p = 0.01$ ) respectively as compared to no follow up with patients after treatment.
- *P. falciparum* patients who received a clear explanation about which medicines were given and what their effects might be were 8.3 times (95 percent CI, 1.22–56.24) more likely to adhere to a single-dose primaquine regimen than those not receiving a clear explanation ( $p = 0.012$ ).
- A cessation of symptoms or forgetfulness were reasons for 48 percent and 17 percent of patients, respectively, for not adhering to primaquine treatment.
- Intrinsic motivations—patients who adhered to primaquine treatment reported doing so because they had a fixed time to take medication or tools to keep track of time (24.6 percent), understood the importance of cure (14.4 percent), or were self-motivated (12.5 percent).

### References

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