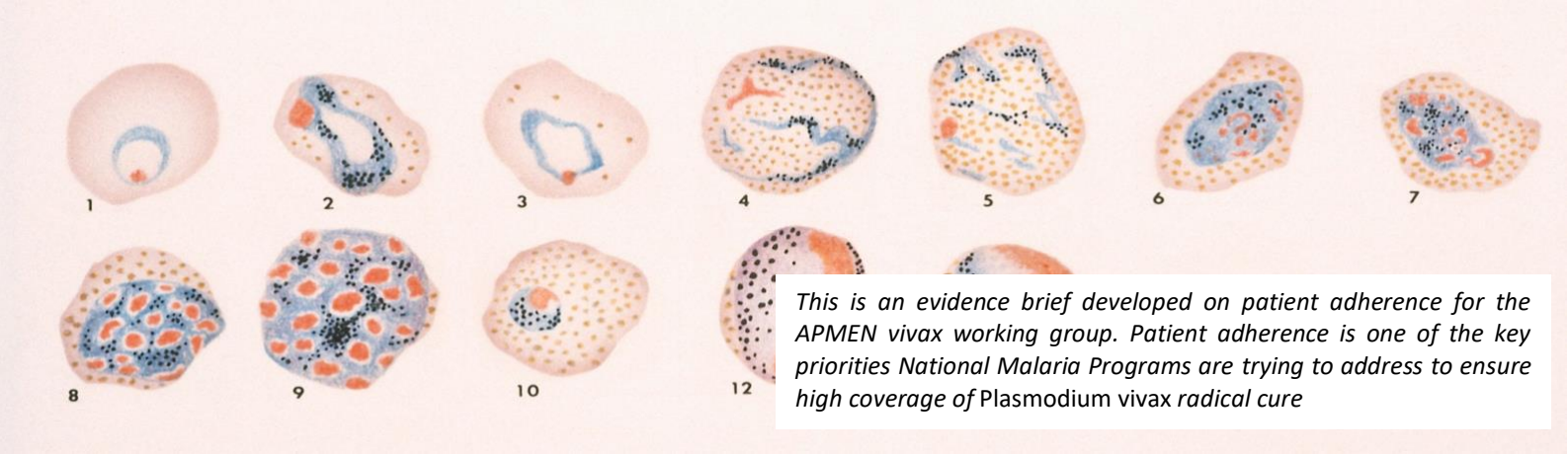


This is an evidence brief developed on patient adherence for the APMEN vivax working group. Patient adherence is one of the key priorities National Malaria Programs are trying to address to ensure high coverage of Plasmodium vivax *radical cure*

An Evidence Brief on Patient Adherence to treatment

Improving the use of* P. vivax *radical cure treatment in the Asia Pacific

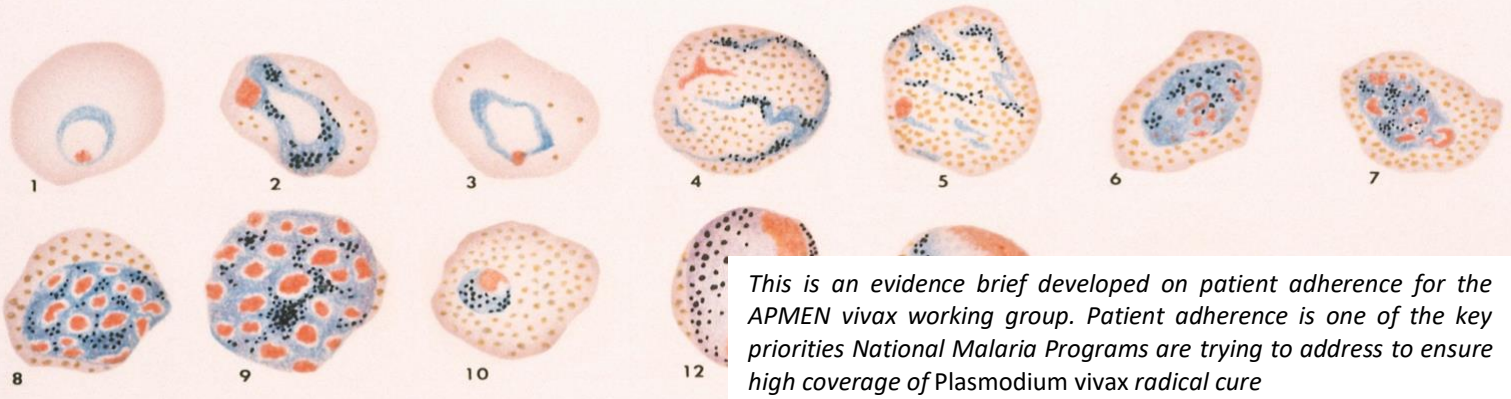
Patient adherence is key for effective treatment. Yet, for malaria, we know from systematic reviews, that adherence even for a three-day treatment can be as low as 30%.[1-3] Currently recommended vivax malaria treatment is a 14-day primaquine (PQ14) regimen for glucose-6-phosphate dehydrogenase (G6PD) normal patients at 0.25-0.5 mg/kg/day and weekly doses (0.75 mg/kg/week) over 8-weeks where patients are G6PD deficient.[4] A single-dose cure, tafenoquine, is on the horizon and offers the potential to mitigate issues with patient adherence. Irrespective, primaquine will remain a treatment option for the foreseeable future, either as a 14- or 7-day treatment while countries consider moving to shorter regimes, as a 7-day course for which evidence is available while countries await WHO recommendations, or over 8 weeks for G6PD patients.

Lack of adherence to medication is not unique to primaquine and vivax, it is a significant public health issue. A recent meta-analysis reported a pooled prevalence of adherence to medication among people with multiple chronic illnesses to be 57.4%, with wide overall range from 16.5% to 93%.[5] In the malaria domain, systematic reviews of adherence to Artemisinin Combination Therapy (ACT) report variable results, but often adherence is poor with some studies reporting adherence lower than 30%.[1,2,6]

Many Asia Pacific National Malaria Programs acknowledge adherence as a major challenge to primaquine use in their country contexts.[7] Limited studies in the Asia-Pacific (India, Indonesia, Papua New Guinea, and Thailand) report large variability of adherence rates to primaquine from 44% to 98%.[8-12]

With most countries in the Asia Pacific striving to eliminate malaria by 2030, treating and reducing the transmission of *Plasmodium vivax*, which has become the more dominant species in the region, is of paramount importance.[13] Due to the dormant liver (hypnozoite) stage, *P. vivax* treatment requires a radical cure that cures both the blood-stage and liver stage infections. Currently, primaquine is the only widely available and WHO-recommended drug against hypnozoites. However, the prolonged administration of PQ for 14 days to 8 weeks brings about issues of adherence with many patients failing to complete the recommended treatment regimen.

This brief aims to collate available evidence on adherence of vivax patients to primaquine radical cure in the Asia Pacific region and draw from the learnings of adherence to medication of other diseases. This brief will be useful to the National Malaria Programs and other



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stakeholders working in antimalarial response in the region to understand the current evidence and improve patient adherence to primaquine by formulating and integrating appropriate interventions into their routine activities.

What is patient adherence?

Patient adherence is defined by the WHO as the "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with the agreed recommendations from a health care provider".[14]

Adherence to medication is a continuous process during which the patient evaluates and re-evaluates the course of his/her illness and the perceived benefits and risks of the treatment.[15] According to the ABC taxonomy, there are three phases of adherence: initiation, implementation, and persistence (Figure 1).[16]

Initiation refers to the starting moment when a patient takes the first dose of the medication after having received a prescription. The implementation phase refers to "the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose is taken". During this phase, adherence may be affected by issues related to taking the medications daily such as specific timing of doses, incorrect food combinations with medication, forgetfulness etc. Persistence refers to the time that patients remain on the prescribed drug regimen from initiation until discontinuation.[17] Discontinuation typically results from a rational decision making by the patient.[16]

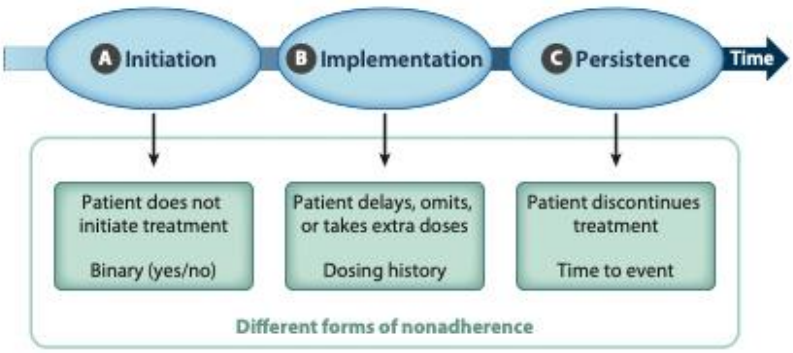
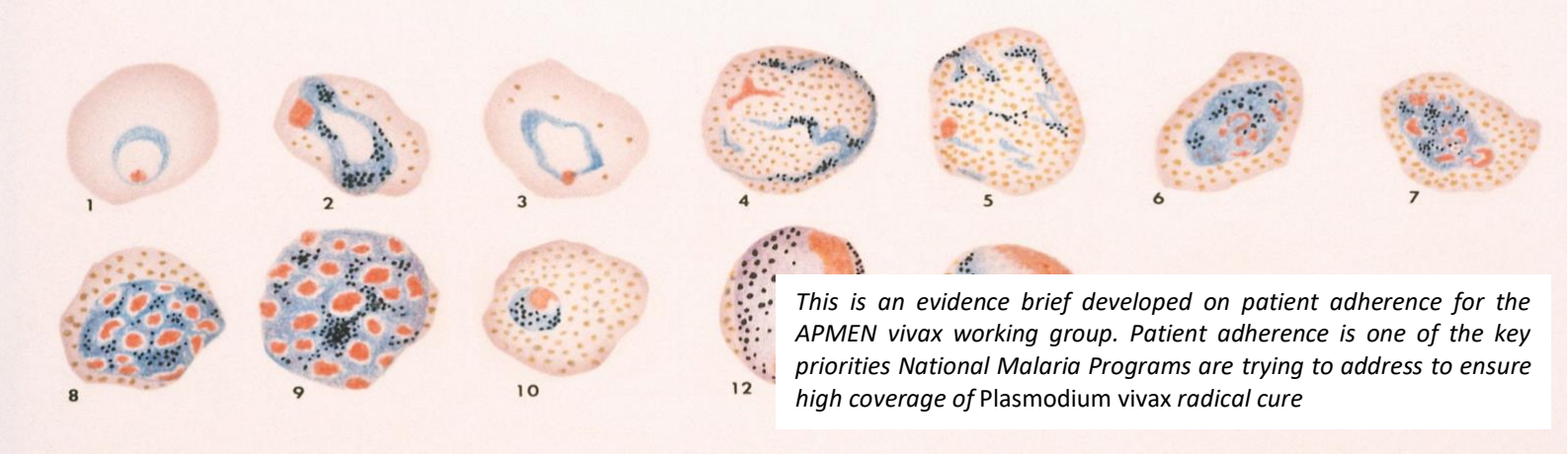


Figure 1. The ABC taxonomy of patient adherence (Source: Zullig et al., 2018)

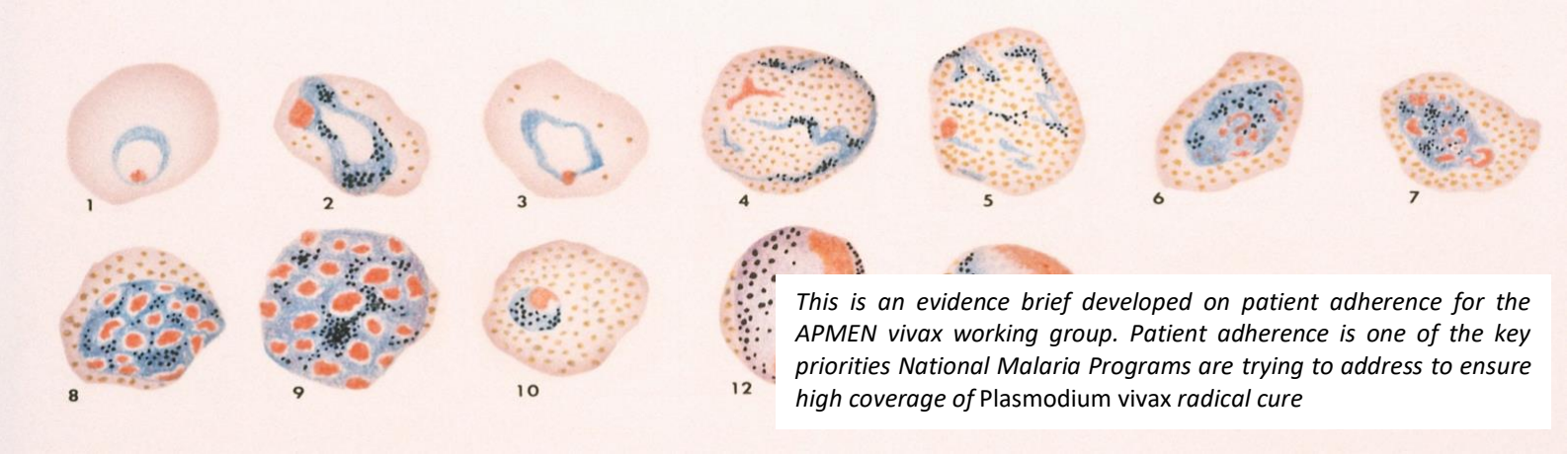
How is patient adherence measured?

There is wide variability in how patient adherence is measured. In a study among 30 medication adherence experts, seven measurement approaches were recommended by the majority of the experts: self-report, prescription fill data, pill count, drug levels, electronic



drug monitoring (EDM), smart technology, and direct observation.[18] These and other measurement methods are outlined in Annex 1.

In summary, the approaches broadly focus on measuring process and outcome-oriented indicators. Approaches such as patient-self report, validated patient scales [for example: Morisky Medication Adherence Scale (MMAS/MMAS-5/MMAS-8), Medication Adherence Report Scale (MARS), and General Medicine adherence Scale (GMAS)] (Annex 2-5), pill counts (manual or electronic), direct observation, and ingestible electronic pills/sensors measure the process of the patient ingesting the medication. In contrast, pharmacological metrics of adherence measure the outcome of an adequate concentration of drug or related compounds in patient's blood or urine. Combining two or more measurement strategies can be beneficial in accurately assessing patient adherence than employing only one measurement approach.



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What factors influence patient adherence?

Patient-related factors such as lack of information, motivation, and strategy to follow the recommended treatment regimen can affect adherence,[19] which can be driven by patient's age, gender, ethnicity, and socio-cultural norms. Patients can be up to five times less likely to be adherent to vivax radical cure when they feel better than when they feel worse.[20] Other factors of patient adherence can include their access to free health services of perceived quality, positive interaction with healthcare workers, and medication characteristics with favorable taste, appearance, and less number of tablets and side-effects.[21]

Holistically, the WHO outlines five broad dimensions of patient adherence as shown in the Figure 2.[14] Several interventions targeting these factors have been identified to improve patients' adherence to medication of many chronic diseases.[14]

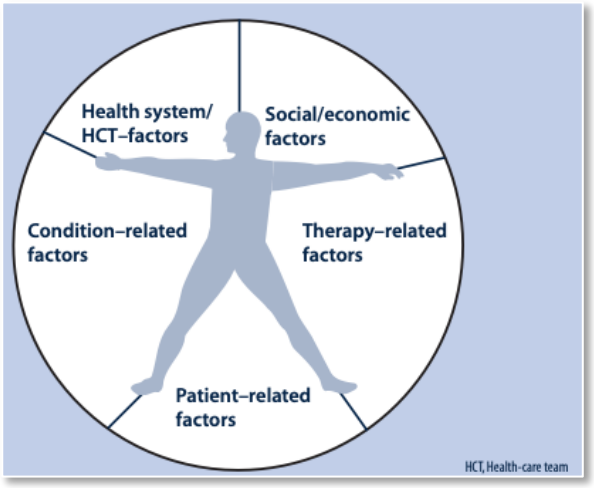
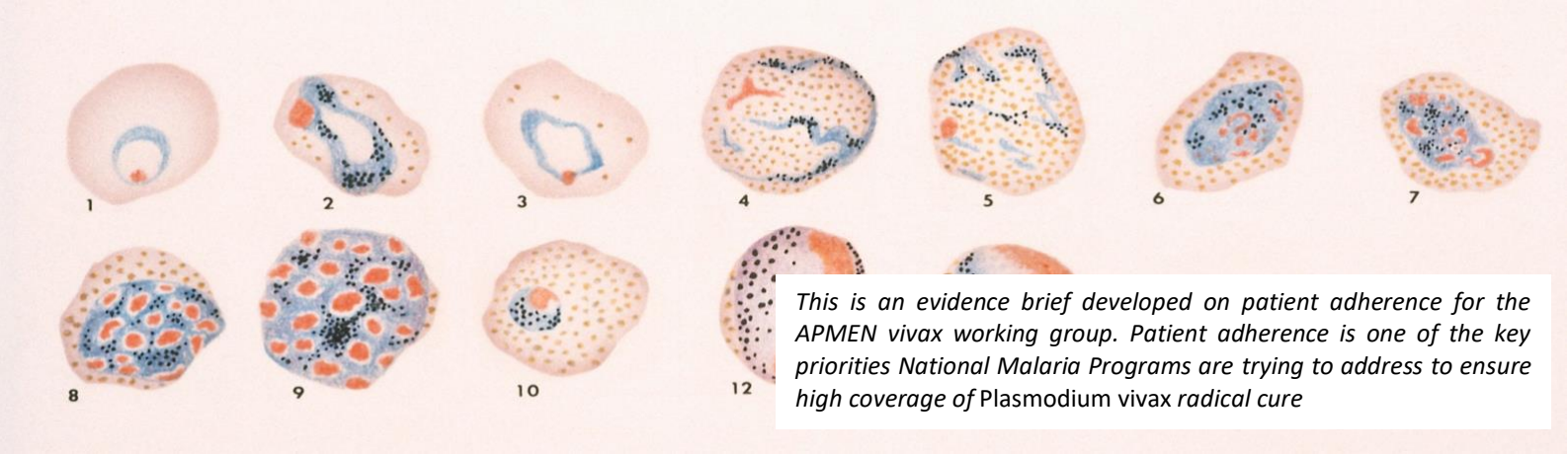


Figure 2. Dimensions of patient adherence (source: WHO, 2003)

What is the evidence for proven interventions for patient adherence?

Using results from systematic reviews and studies conducted in different countries, interventions with significant efficacy in controlled settings or effectiveness in real-world settings are highlighted in this section. The impact of the interventions can be influenced by differences in the quality of care received under trial and routine conditions.[22]

The interventions have been described in this section an order that reflects the patient pathway such that the interventions directed at the patients are described first, followed by interventions improving patient-healthcare worker relationship, and then the broader community level interventions.



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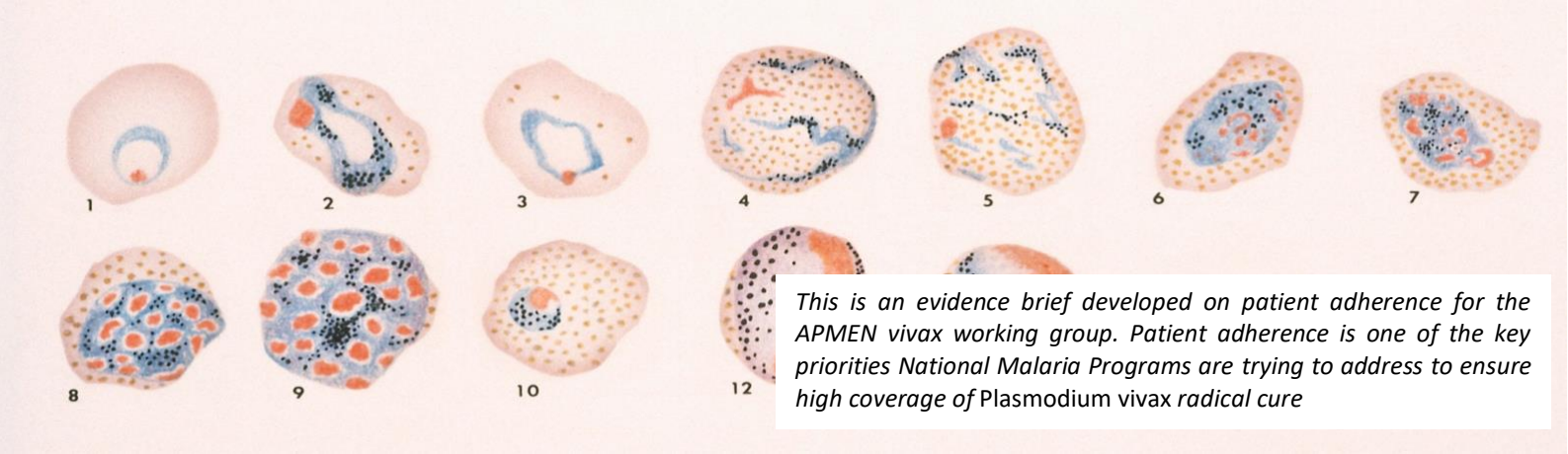
A. Interventions targeting the patient-healthcare worker relationship:

Training healthcare workers in communication skills

The interaction between the healthcare providers and patients plays a critical role in the quality of health care and can be a determinant for patients' adherence to their medication. Healthcare workers with fewer years of training such as community health workers in low- and middle-income countries often have poor communication skills.[23] In Laos, one study found that more than a quarter of healthcare workers did not regularly explain the importance of completing the antimalarial regimen to patients, and nearly one-third of them did not confirm the patients' understanding of medication instructions.[24] Improving interpersonal communication between the patient and the healthcare worker is therefore vital to increase adherence to antimalarial drugs.[25]

There are some evidence that show that better communication between the patient and their healthcare provider can lead to better patient adherence:

- In a meta-analysis, training physicians in communication skills resulted in higher patient adherence by an odds of 1.62 when compared to physicians with no training.[26] The same study also found that there was a 19% higher risk of lack of adherence among patients whose physician communicated poorly than among patients whose physician communicated well.[26]
- Among caregivers of children with uncomplicated malaria in Sierra Leone, positive interactions with the healthcare providers who took the time to examine their children and explain how to administer ACTs carefully, were facilitators of adherence to ACT.[21]
- Better counselling, practical demonstration of how to give the medicine; the longer time spent with the health care provider and the focus of the provider on ensuring that the caregiver understood the instructions were influential in adherence to paediatric malaria treatment in trial settings in Kenya.[22] However, the participants reported that their experiences during the trial were considerably different to the care they received under routine conditions
- Addressing language and culture barriers are important in the patient-healthcare worker relationship. Some studies suggest using communication strategies such as checking patient understanding of dosage instructions and explaining jargon terms, and having trusted and trained third parties in the healthcare teams to assist with achieving cultural brokerage, patient support and patient education.[27,28]
- Culturally adapted motivational interviewing may be effective in improving adherence with the ethnic groups.[29]



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B. Interventions targeting the patients:

Patient education

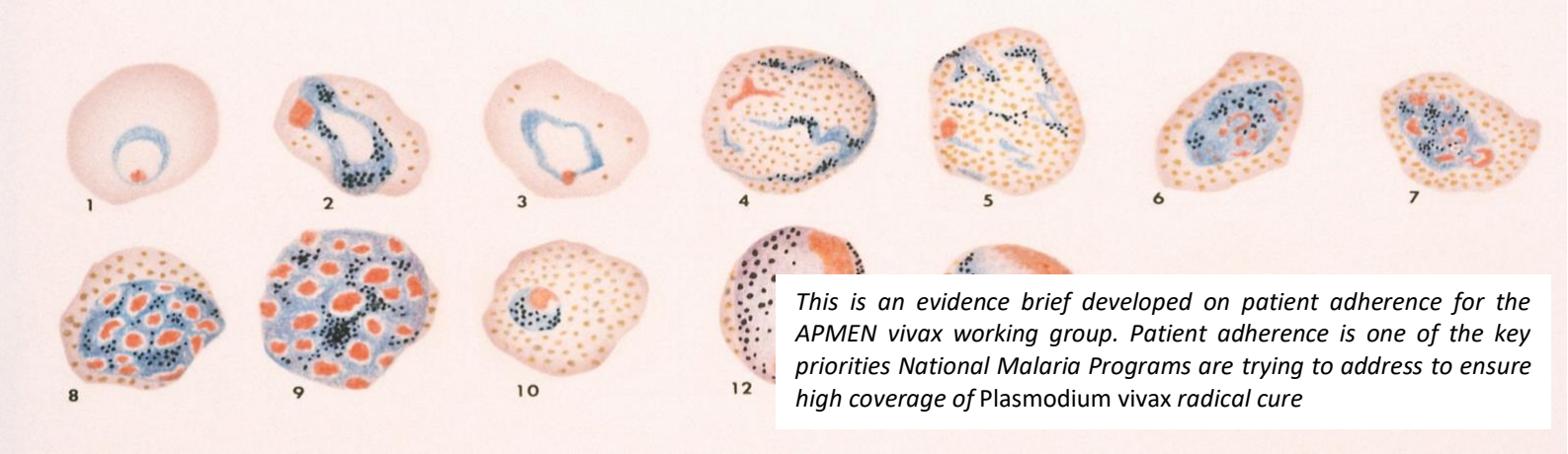
Patient education has been a standard approach to counsel patients and give them the necessary information regarding the disease and medication.

- Targeted behavior change communication using the Information, Motivation, Strategy (IMS) Model may help in promoting adherence to the patient during their visit to the healthcare center.[19]
- A similar strategy of providing information, education, and communication (IEC) through participatory learning and action methods was found to increase the adherence of vivax malaria patients in Northern Thailand to PQ14, with 71.1% of the patients in the intervention group completing their prescribed treatments compared to only 29.9% of the patients in the control group.[30]
- Adherence to ACT among falciparum malaria patients was significantly higher (81%) in those receiving IEC compared to controlled patients not receiving IEC in a study in Cuttack, India.[31]
- In another study at the public health centers in Mae Hong Son, Chiang Mai, and Chiang Rai provinces of Thailand, a patient education program which also focused on interpersonal communication significantly increased vivax patients knowledge, perception, and their awareness to comply with drug adherence.[32]
- In a study that evaluated the impact of printed materials designed to instruct patients in communication skills, training patients using a booklet had a noticeable but statistically insignificant effect on medication adherence.[33]
- Patient education intervention may be more effective in improving patient adherence when combined with other interventions such as self-management skills training, counseling, or as part of healthcare worker-delivered packages of care.[34]

Improved packaging of medicines

Improving the packaging of antimalarial medications through blister packing and pre-packaging the unit doses in a user-friendly way can optimize their use and improve adherence.[35,36]

- A randomized controlled trial in PNG reported a trend towards better adherence of patients with pre-packaged antimalarial drugs compared to bulk packaging (66.7% vs 58.3%).[11]
- Blister packaging have worked well to worked to improve adherence to antimalarial drugs in South-East Asia and the increased cost of packaged medication did not limit the use of the antimalaria drugs.[37]



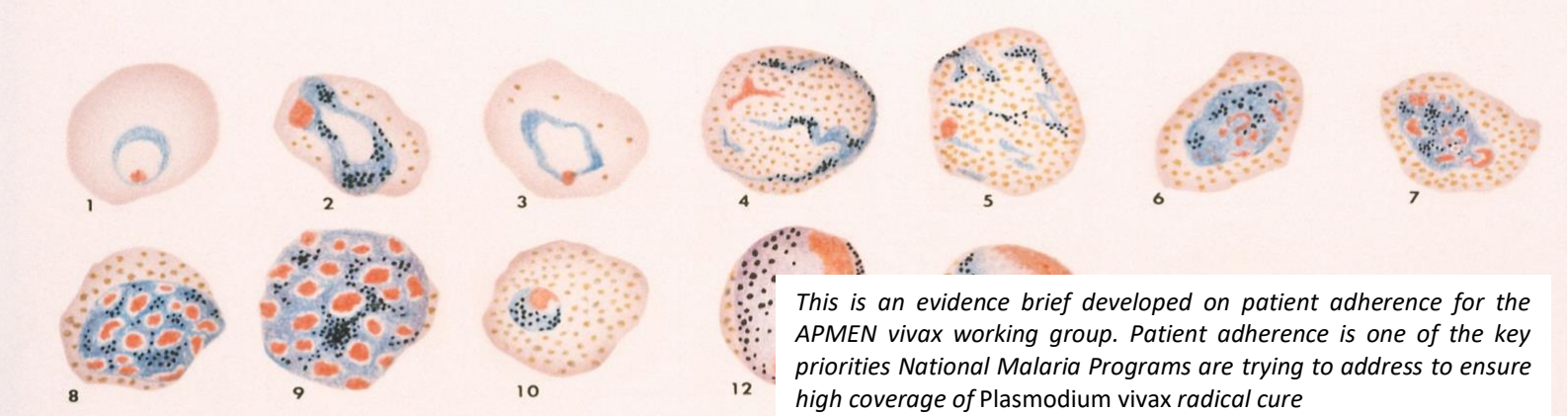
- For example, in rural Myanmar, patients buying a combined blister packaged 5-day course of artesunate and mefloquine with marked daily doses had an adherence rate of 99.5% (378/380).[38]
- Blister packaging significantly improved adherence of 3-day and 8-day PQ over traditional means of dispensing antimalarial drugs in a paper envelope in a clinical trial in China.[39]

- Evidence from Africa also show that blister packing and pre-packing can improve adherence, especially among the caretakers of children:
  - In Uganda, blister pre-packaging was considered useful by the caretakers of children with malaria.[40] In addition, a recent study showed that stickers with short, targeted messages on the packaging increased adherence by 9% and reduced untaken tablets by 29%.[41]
  - In Ghana, pre-packed CQ tablets had 91% adherence with children (through the caregivers) compared to 42% who were provided syrup only.[42] Similarly, adherence was found to increase by nearly 20% in both children and adults with CQ tablets prepackaged into unit doses than those prescribed in envelopes.[43]
  - Patients receiving instructions in the medication package as a visual aid were 2.5 times more likely to adhere to antimalarial treatment in a cross-sectional study in rural Malawi.[44]

Patient reminders

Timely reminders to patients during the course of their treatment can be beneficial in improving their adherence to medication.[34]

- One such reminder strategy can be using the short messaging services (SMS) through mobile phones. A meta-analysis has shown that SMS reminders can significantly improve childhood immunisation coverage and timeliness in low- and middle-income countries.[45]
- SMS messages were effective dosing reminders for participants of a clinical trial in western Kenya as reported in a qualitative study.[22]
- In Malaysia, a mobile application was found to be useful and reliable to assist in improving medication adherence.[46]
- Reminder-based interventions resulted in an average patient adherence of 66.6% vs 54.7% among control groups who did not receive any reminders in another meta-analysis.[47]
- In a randomized controlled trial, twice-monthly telephone calls to patients from a nurse increased medication adherence by 9% for hypertension.[48]
- However, a patient reminder intervention through interactive voice calls via mobile phones in Bangladesh *did not* show a statistically significant effect on diabetes type 2



medication adherence as both intervention and control group had more than 90% self-reported adherence at the start and end of the randomized clinical trial.[49]

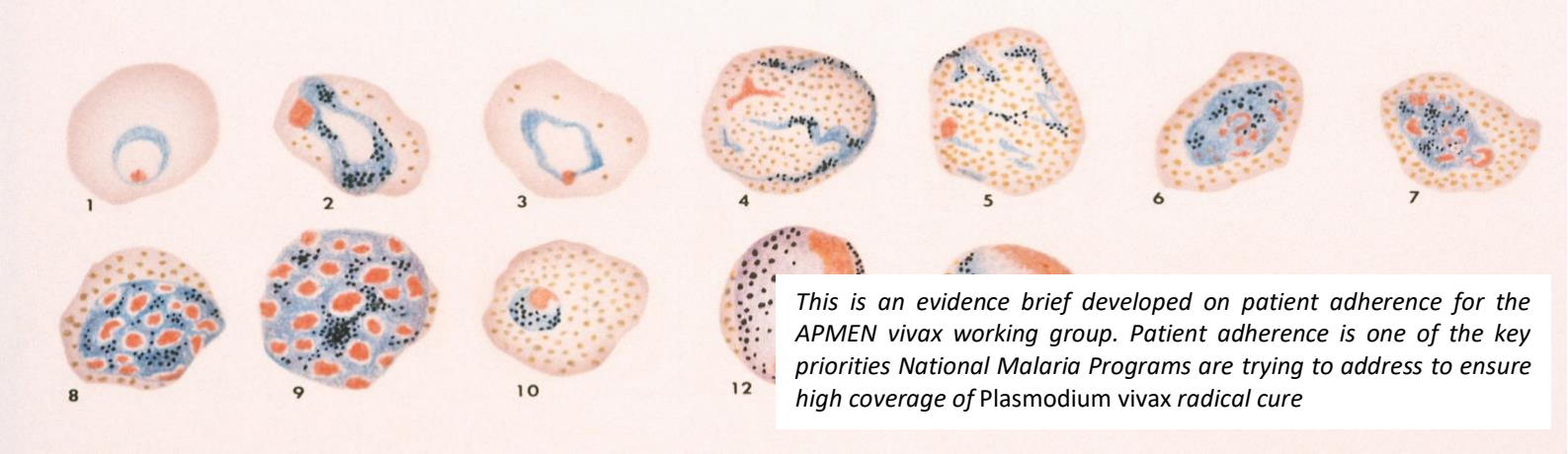
Medication supervision

Few studies in Asia Pacific show that unsupervised administration of primaquine according to the WHO guidelines can lead to less than 30% patient adherence[12] and ineffective reduction in the risk of clinical recurrence of vivax.[50,51] There are different strategies to supervise the patients' intake of medications during the course of their antimalarial treatment to ensure adherence. They have been described below:

Directly observed therapy (DOT)

DOT is widely used as the standard of practice for ensuring patient adherence, particularly for tuberculosis.[52] DOT is the practice of routinely observing the patient swallow all of their medications.

- DOT can be achieved for antimalarial treatment either through admitting patients in the hospital for the duration of their treatment, requesting patients to return for treatment each day, directly observing patient treatment each day at community level through community health workers, or supervising patients remotely through telephone or video every day.
- While DOT is recommended for primaquine regimen by policy in Asia-Pacific countries such as North Korea, Myanmar, Thailand, Timor-Leste, China, Malaysia, Philippines, Vanuatu and Vietnam,[53] its implementation is lacking and there are limited scientific evidence for its efficacy in improving adherence to PQ.[54]
- In one clinical trial at the Thai-Myanmar border, DOT achieved 100% PQ14 adherence rate which was higher than that in the self-administration group (80.4%). Subsequently, vivax reappearance rate was significantly lower in the DOT group than the self-administered group (3.4/10,000 person-days vs. 13.5/10,000 person-days, p = 0.021).[51]
- Another trial along the Thai-Myanmar border in Ratchaburi, Thailand suggested that adherence to PQ14 with DOT increases the effectiveness of primaquine treatment, especially in remote malarious areas.[55]
- In northeast Myanmar, CQ-PQ14 provided as DOT had a high efficacy with only 2.6% (7/260) recurrence rate of parasitemia.[56]
- In Sri Lanka, most malaria cases (in the military) towards the end of the elimination phase were kept under DOT in barracks until treatment with 14 days of primaquine was completed. During the elimination phase, all *P. vivax* cases were treated with primaquine under supervision to ensure full adherence.[57]



- However, there are some studies that suggest that unsupervised treatment with patient education during routine clinic visits may equally have as high adherence as supervised treatment in malaria-endemic settings.[8,58,59]

Semi-supervised treatment

Partially supervised treatment with direct observation of the patient on few scheduled days is an alternative to DOT which is fully supervised. Some examples of semi-supervised antimalarial treatment are:

- In Indonesia, a recent trial found that 89% of patients supervised to take PQ every alternate day (via home-visit to provide PQ tablets for that day and the following day) took 5 mg/kg or greater of total PQ compared to only 64% among unsupervised patients. Supervision of primaquine radical cure treatment also reduced the risk of *P. vivax* recurrence in the study.[60]
- In Ethiopia, the efficacy of PQ14 with supervision on days 2,3,7,10 and 14 was three to four times higher than that of unsupervised PQ14 for vivax recurrence.[61]

Video- and Digitally observed therapy

Newer techniques of supervised treatment include observing patients remotely either through videos or digital adherence technologies (DAT), thereby reducing the implementation costs and ethical issues associated with DOT for the healthcare worker, and decreasing the opportunity cost and increasing the convenience for the patient.[62]

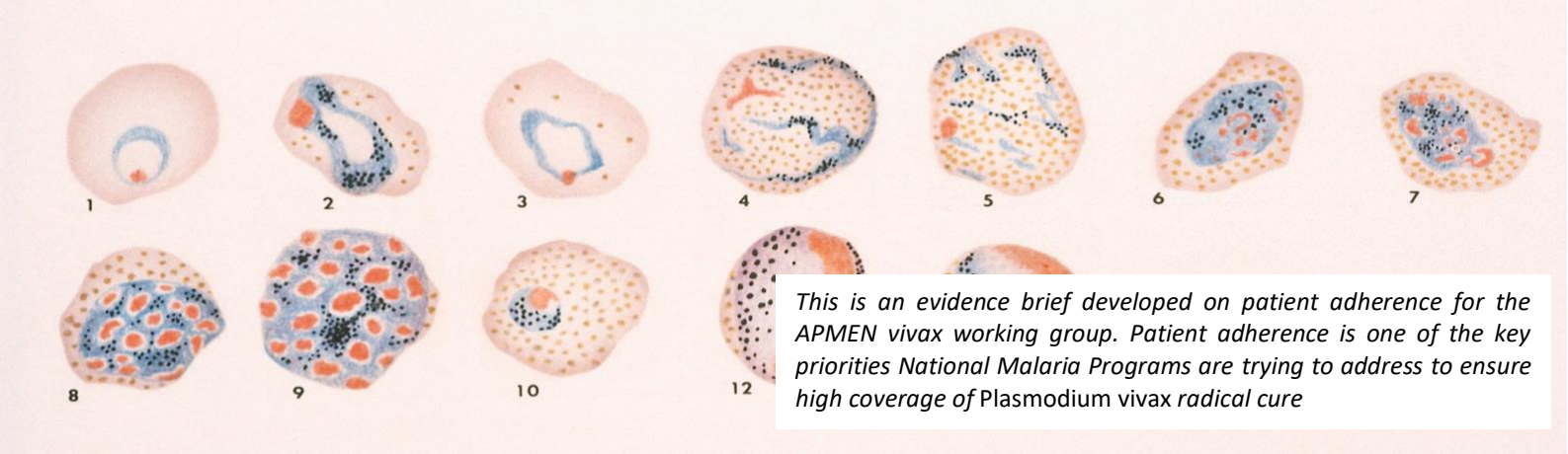
- DATs feature phone-based and smartphone-based technologies, digital pillboxes, and ingestible sensors that may facilitate more patient-centric approaches for monitoring adherence, particularly for tuberculosis.[62-67]
- Potential challenges of these digital techniques are technical issues which can arise, especially for illiterate and less technology-savvy patients,[68] and issues with privacy and confidentiality of the video observed therapy.[69]

C. Interventions targeting the community:

Community education with multiple component interventions

Community-level interventions with multiple components such as mass IEC using visual aids like posters and video clips, and trainings have been shown to improve community members' adherence to medication.[54]

- In Cambodia, an intervention in which posters were displayed at different places in the village such as schools, temples, clinics, pharmacies, army camps and others, along with showing videos in video parlors, restaurants, and at ceremonial gatherings, was found to increase adherence to 7-day quinine and tetracycline antimalarial regimen from 0.5% to 20%.[70]



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- The same study also highlighted that using posters alone was not a significant community-level intervention to increase patient adherence.[70]

- In Mali, an intervention that involved training the managers of drug kits, recruited from the community, on dosage, counselling, and referral, along with the provision of a referral mechanism and visual aids, and a community-level meeting to explain to community members the improvements made to the village drug kits and encourage people to seek treatment from the managers of the kits, significantly improved correct home-administration of CQ for three days by parents to their sick children (68.9% vs. 24.4%) and increased adherence to CQ (71.7% vs. 21.6%), compared to that in the comparison group.[71]
- However, no significant increase was observed in adherence to ACT in Kenya, when a community-based intervention of providing subsidized packs of pediatric ACT to retail outlets, training of retail staff, and community awareness activities was tested in a cluster-randomized trial.[72]
- A systematic review by Fuangchan et al., suggested that more than one potential intervention should be added on top of the existing ones to summate their beneficial effects in the real world. They implied that a combination of community education and a visual media/verbal information can increase adherence to antimalarial drugs.[54]

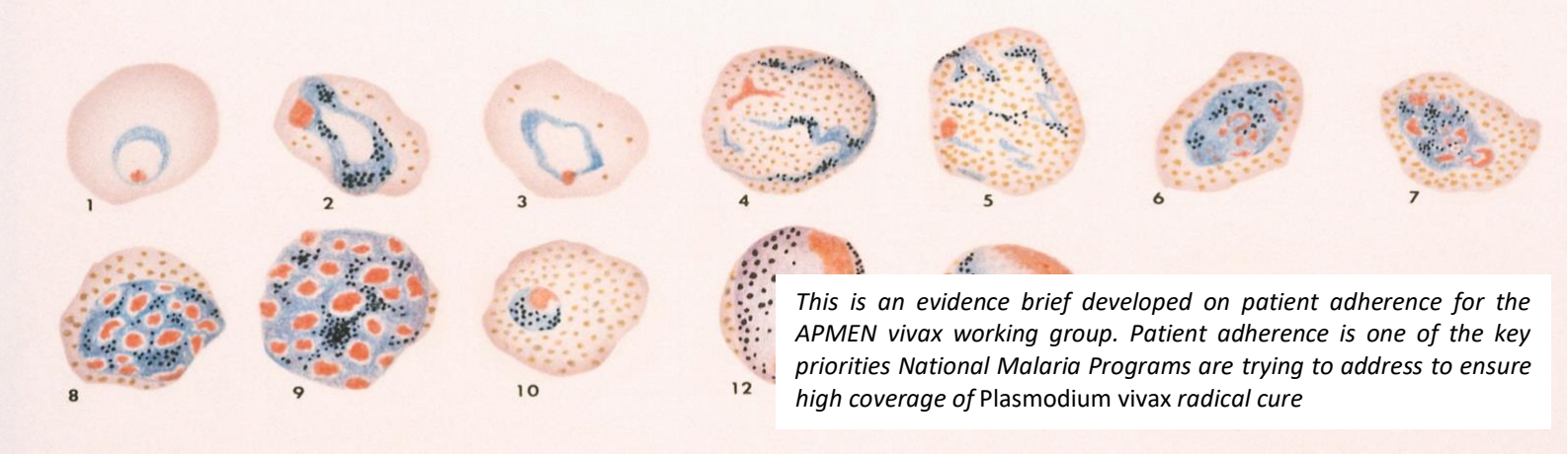
Community mobilization

In China, health staff delivered anti-malarial drugs to each household supported by social mobilization to promote community engagement and adherence in the elimination phase. Involvement of local administrative officers, village health workers, and malaria control workers in community mobilization increased villager's adherence with the intervention.[73]

What are national programs in the Asia Pacific doing to address adherence?

Individual patient counseling at point of care and community level on primaquine regimen and the importance of adherence as part of routine vivax case management –

- In Vietnam, community malaria action team (CMAT) staff provide one-on-one counselling to patients
- In Laos, health centers counsel patients about radical cure including G6PD test result, which regimen the patient will receive, the impact of not completing full course of PQ to the family's economic and time as well as to the district and province; and the village malaria workers (VMW) counsel the patients regarding how to complete the treatment on the day of follow-up.
- In Cambodia, VMW and Health centers provide counselling to vivax or mixed infection patients



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Patient reminders:

- *Patient cards* – In Cambodia and Laos, cards are given to patient and collected after 14 days for data entry to ensure adherence
- *Pillbox* – In Vietnam, PSI has a small-scale PQ pillbox initiative in which patients receive a box containing 14 day of PQ. When patients open the box, a notification will be sent to health care staff. When the healthcare staff do not receive a notification, they will send a reminder to the patients.
- *PQ box reminder sticker* – In Thailand, a reminder sticker is placed on the PQ pill box

Medication supervision by family member:

- In Thailand, community health workers help to educate the patient or advise a family member to supervise daily PQ and complete the regimen**.** This method has helped the doctors in the hospital to convince patients on adherence to PQ14.

Patient reminders and semi-supervised treatment

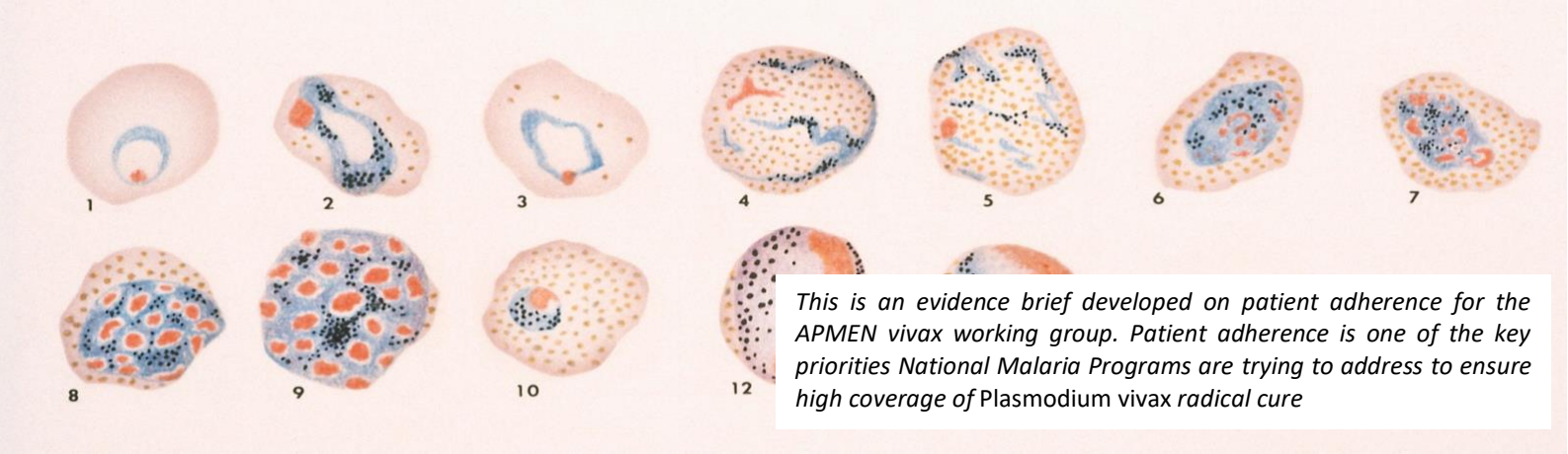
In the GMS, patients are either reminded by phone calls and/or supervised during household visit on select days:

- In Vietnam – a local NGO (SCDI) uses a follow-up form and HCWs physically follow-up with the patient in some areas
- In Laos, in a pilot phase, VMWs provide daily/weekly follow-up (day 3,7,14 for PQ14 and weekly for PQ8weeks) in person or by phone and both the patients and VMW receive financial incentive for complete referral and adherence
- In Thailand, malaria post workers (MPWs), village health volunteers (VHVs), and local CSOs (in border areas) help reach out to follow-up patients in remote villages.
- In Cambodia, health center staffs follow-up the patient by phone calls (or in-person visits) and the VMW via in-person household visit on Day 3,7, and 14.

What are further strategies that can be used by national programs and partners to improve patient adherence?

Where possible, consider shorter regimens of primaquine (PQ7) and single-dose Tafenoquine (TQ)

- Shorter radical cure options like PQ7 significantly reduce the treatment duration and may improve adherence. A multicentric randomized controlled trial in India demonstrated significantly better adherence when the PQ regimen was reduced from 14 days to 7 days.[74]
- Single dose TQ removes the possibility of improper implementation of the dosing regimen, and discontinuation of the treatment, thereby addressing major adherence issues.



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- The availability of tafenoquine and, perhaps PQ7 is reliant on the availability of semi-quantitative G6PD testing where patients are treated. NMPs could consider introduction of G6PD testing in pilot areas to determine feasibility of its use.

Better drug formulations

- Availability of pediatric formulations and dosage forms of PQ will eliminate the inconvenience of having to manually break the adult dose tablet into smaller portions for administering to child patients, thereby improving the drug administration and indirectly the adherence.[75]

Review case management training to ensure inclusion of Interpersonal Communication approaches by health workers

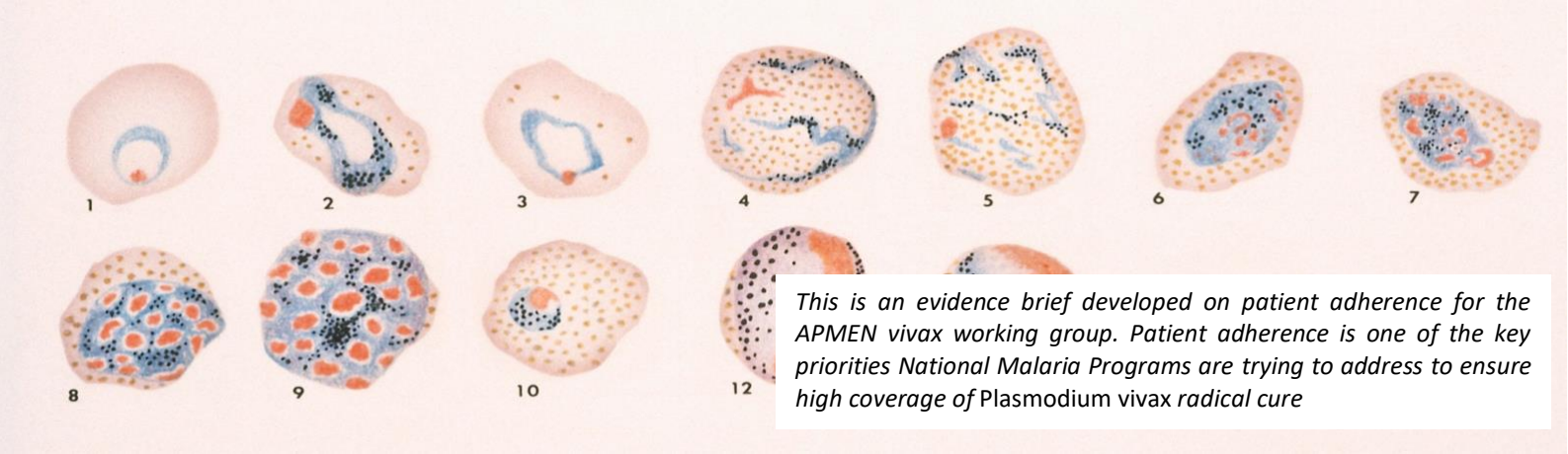
- Interventions that foster a good patient-provider relationship, train health workers and develop a system to supervise and follow-up patients may improve adherence.
- The vivax case management training can include sessions on improving healthcare workers' patient counselling through better interpersonal communication, using culturally-adapted motivational interviewing techniques, spending more time with patients, giving practical demonstrations, and checking patient understanding of dosage instructions.

Promote use of PQ/TQ with food to decrease possible gastro-intestinal side effects

- PQ can cause gastrointestinal side effects that may lead to lack of adherence to drug treatment.[76] Healthcare workers can guide patients for the appearance and the transience of such side effects in order to avoid abandoning treatment. Promotion of taking PQ with food during patient counselling or education can enable patient to not only incorporate the medication into their daily routine activity, but also help prevent gastro-intestinal side effects of PQ which might dissuade some patient to continue taking it.[77]
- TQ should also be given with food to reduce possible gastro-intestinal side effects.

What should we know about the evidence quality?

Despite many interventions being used and studied, there is a lack of strong evidence base for approaches to improve patient adherence. A major limitation in the studies is that the evidence is reliant on clinical trials that may provide information on the efficacy of adherence intervention, but do not provide information of effectiveness in the real world settings. Effective intervention policies will require deeper consideration of socio-cultural factors and practical challenges that underlie adherence.



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Other limitations include the interventions not being targeted to specific phases of patient adherence. For example, issues with discontinuation, typically the result of rational decision making by the patient, need different interventions than issues in the implementation phase, which are often the result of forgetfulness or disruption of routines. Thus, interventions that target attitudes and knowledge might be more helpful in the case of discontinuation. Reminder systems have more value during the implementation phase, although rational decision making might also drive behavior during the implementation phase. The current array of tools available to clinicians and researchers is not sufficiently specific to target solutions to adherence phase(s) or barriers.

There is also a need for multilevel interventions as most adherence interventions focus exclusively on the patient level. Interventions targeting health care providers, organization of health care delivery, and health care systems, and the larger health policy context are warranted as patient adherence is a multidimensional phenomenon. A package of context-specific strategies approaches has the greatest potential to bring about behavior change in the affected communities rather than one single intervention.[78]

Finally, accurately reporting which factors are being intervened upon, at what stage the factors are targeted using the ABC taxonomy,[17] taking into consideration the intervention components (Figure 3) put forward by Michie et al.,[79] and conducting rigorous implementation research are all necessary to ensure successful implementation and scale-up of adherence interventions.[16]

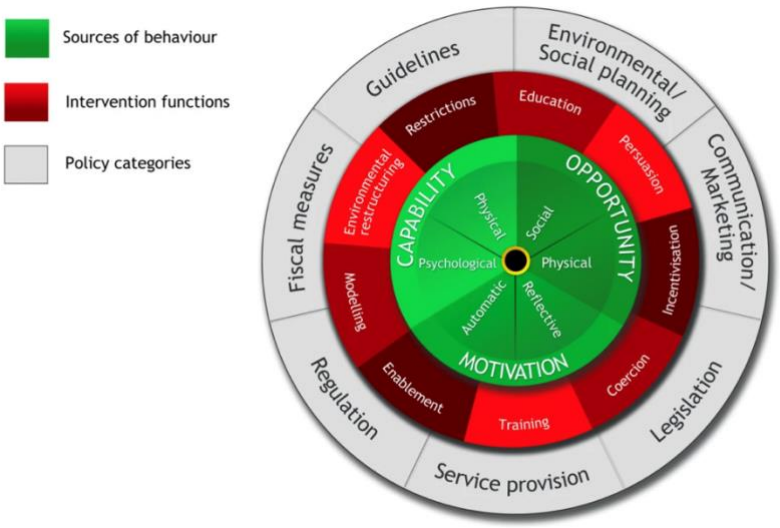
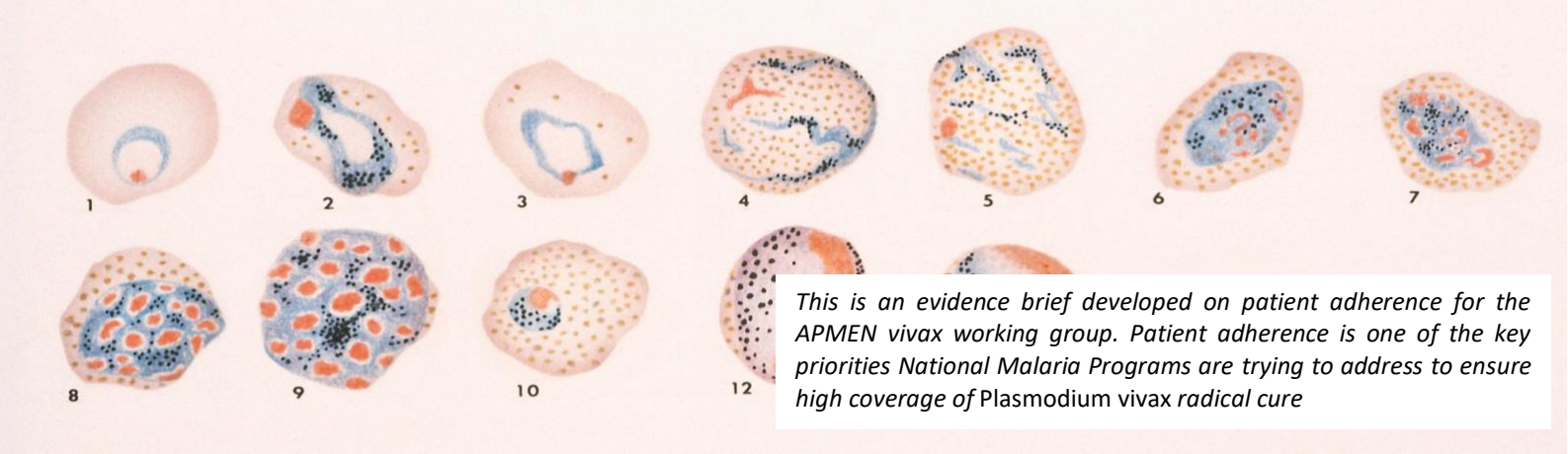


Figure 3. The Behaviour Change Wheel (Source: Michie et al., 2011)



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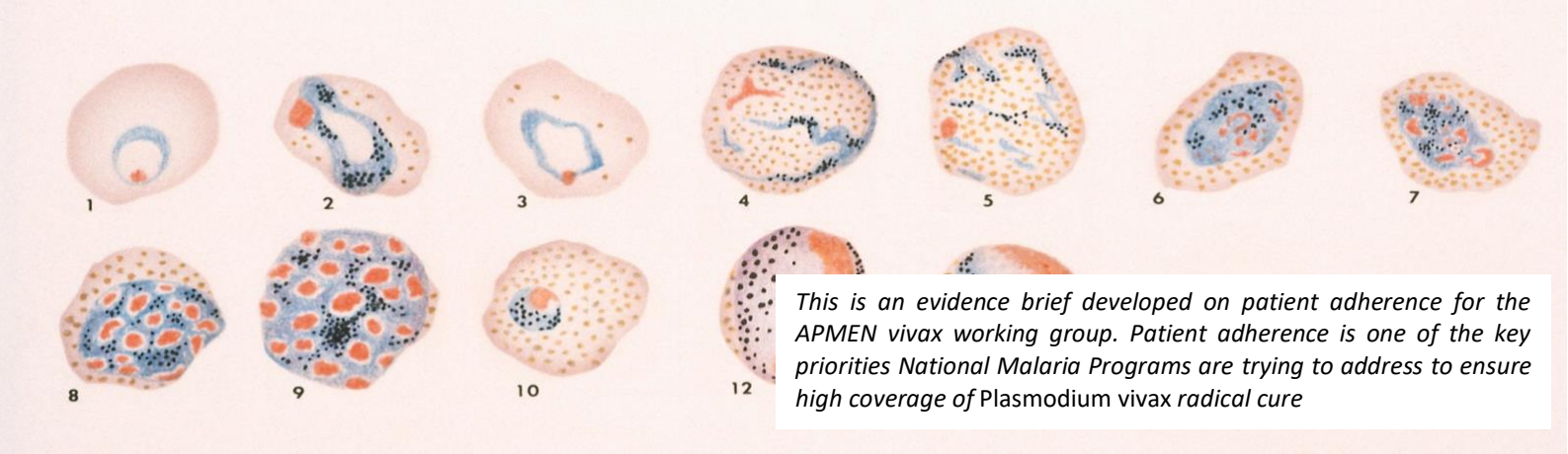

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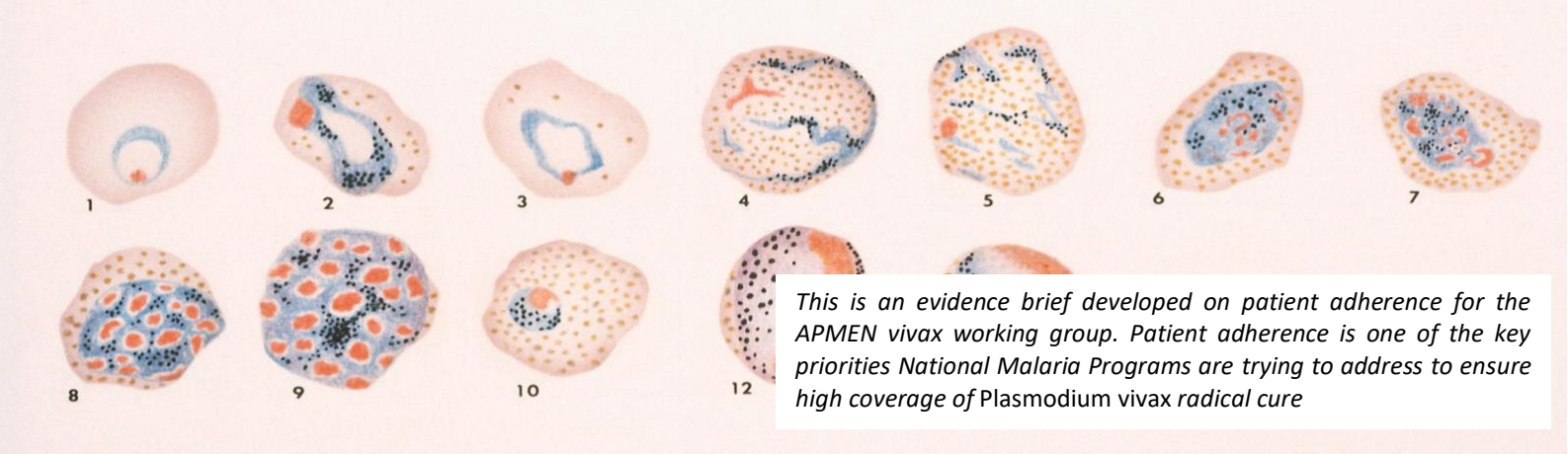

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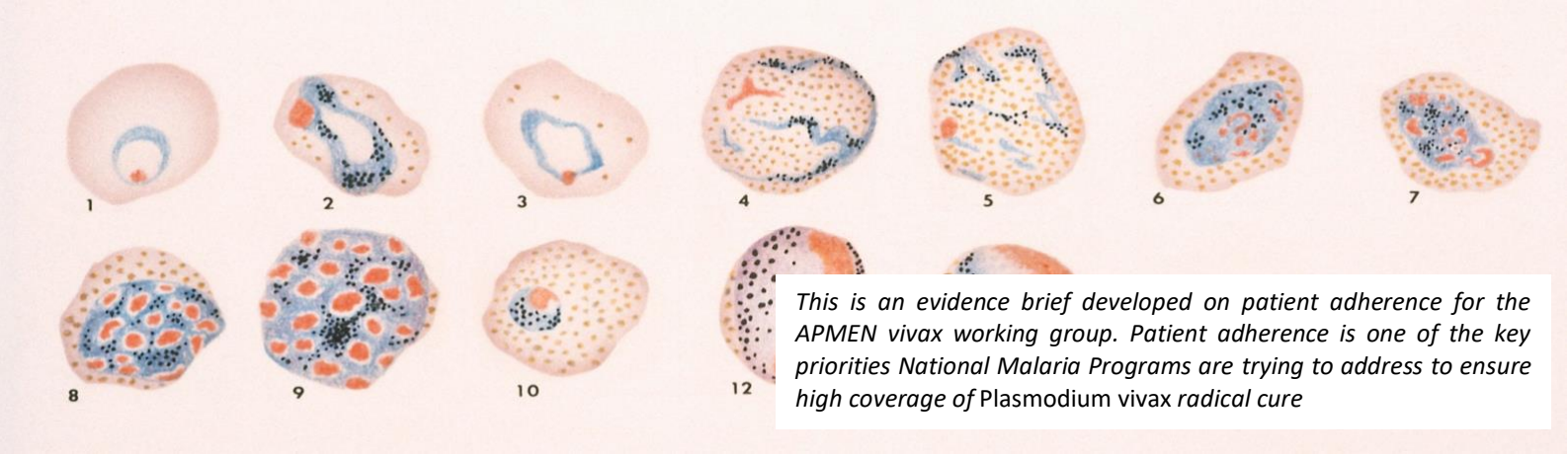

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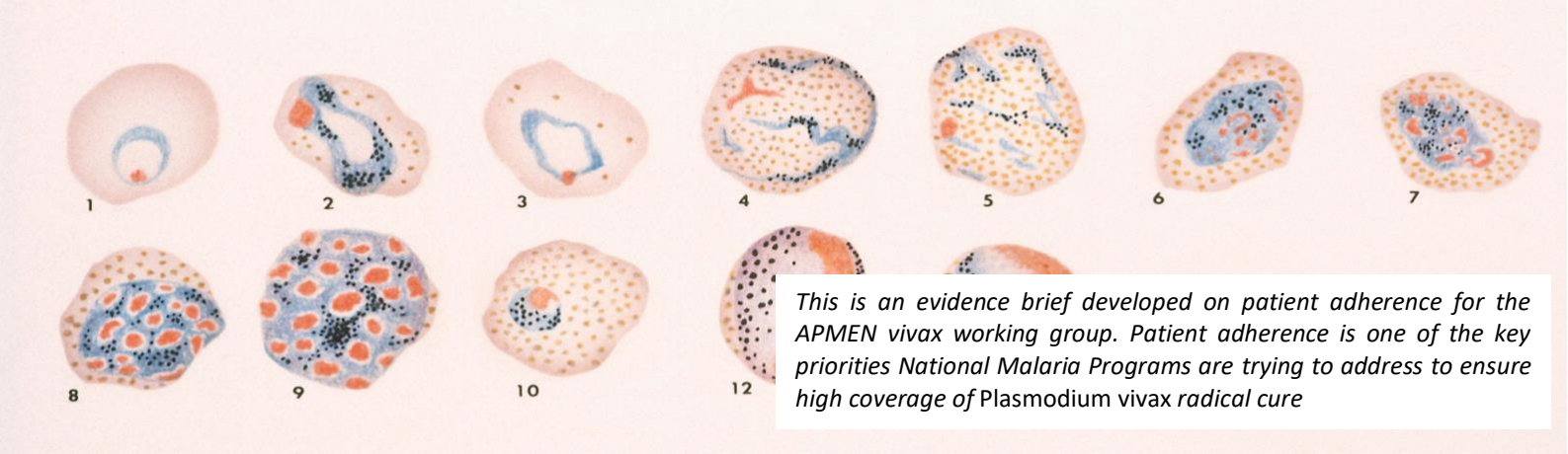

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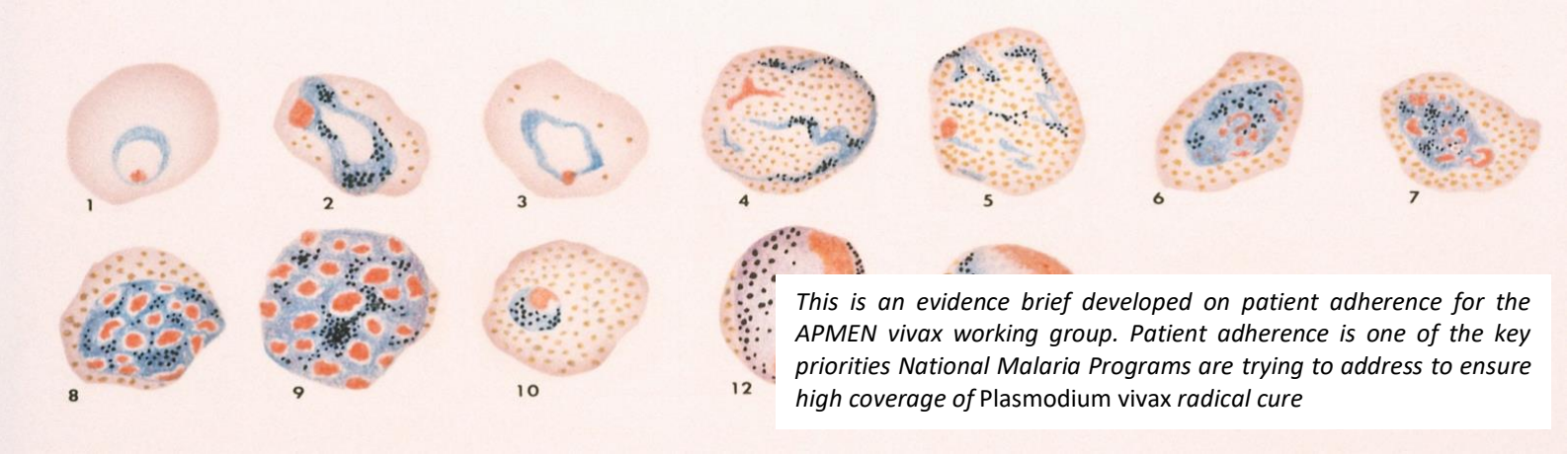

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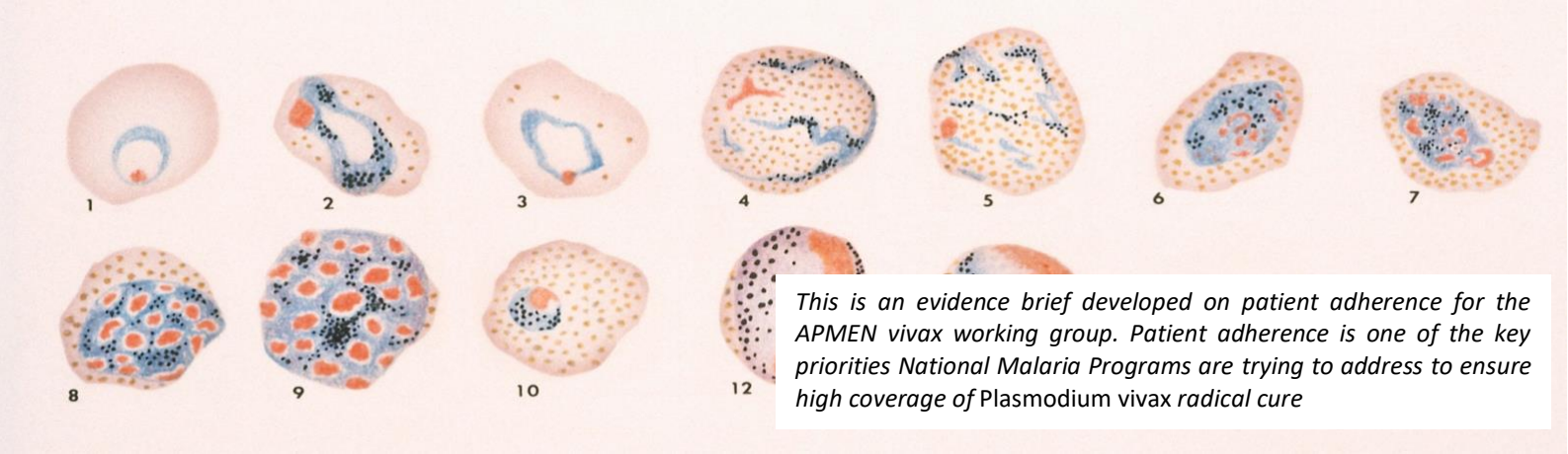

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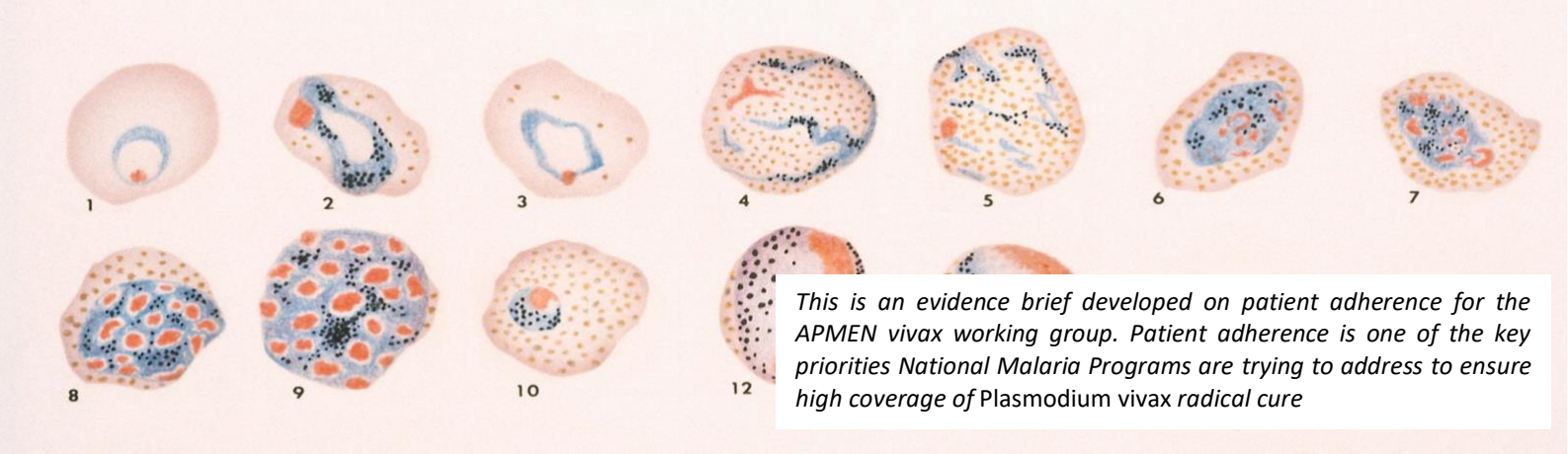

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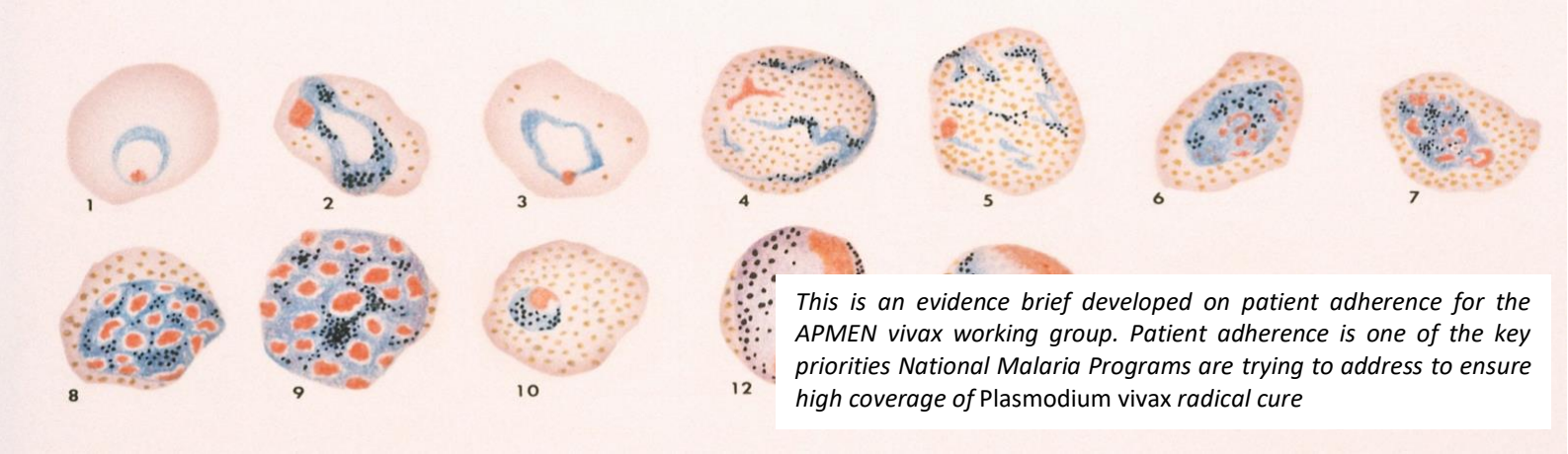

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Annex:

Annex 1: Overview of methods for measuring patient adherence

	Method	What is it?	Reliability & validity
Process oriented measures	Patient self-report	• Self-reporting is where a patient is actively asked about the treatment they took and whether they completed. This is a widely used method to measure adherence	• This method is highly subjective, dependent on how questions are asked, and prone to recall and social desirability bias, where patient tends to give the expected answers.[78] • Self-report can overestimate adherence, compared to pill count or biological assays.
	Patient-reported outcome measures (PROMs)	• Various patient-reported outcome measures (PROMs) have been developed to measure self-reported adherence to medications. • These PROMs may be useful in clinical practice because they are easy to administer. • Based on the patients' PROM ratings, health care professionals may be able to provide timely feedback. Thus, underlying issues that contribute to medication noncompliance can be addressed at the point of care.[80] • Kwan et al (2020) identified 121 unique patient reporting forms used in 214 studies of which the most commonly used are; the	• PROMs have been evaluated for their; ○ Validity and reliability e.g. through measuring convergent and discriminant validity[1] ○ Internal consistency using a Cronbach's alpha value ○ Inter-rater reliability, composite reliability, and intra-class correlations • PROMs with at least a moderate level of evidence for >=5 measurement properties include the ASK-20, CQR, General Medicine Adherence Scale (GMAS), Hill-Bone Scale, ITBS, MAR-Scale revised, MARS-5, MARS-9, MMAS-4, MMAS-8, SEAMS, SICT, TAI, and questionnaire by Voils.

[1] Convergent validity takes two measures that are supposed to be measuring the same construct and shows that they are related. Conversely, discriminant validity shows that two measures that are not supposed to be related are in fact, unrelated

		Morisky Medication Adherence Scale (MMAS/MMAS-8), the MMAS-4 and the Medication Adherence Report Scale (MARS).[81]	• Of these, only the GMAS has sufficient (+) ratings for at least four measurement properties.
	General Medicine Adherence Scale (GMAS)	• Several psychometric tools have been formulated to measure non-adherence to medications in patients; however, no tool has originated from developing countries. • The GMAS, developed in Pakistan, is the only tool to incorporate a domain on cost related non-adherence (CRNA) that may be more pertinent in low resource settings.[82]	• The GMAS was estimated by Kwan *et al* to have sufficient ratings for at least four measurement properties.[81] • The convergent and discriminant validity was measured.[82] • Cronbach's alpha was measured as 0.84 compared to 0.7 as measured with MMAS-8 in the same context • For inter-rater and composite reliability and intra-class correlations all items on the scale were positively correlated with each other with moderate to strong correlations • The test-retest reliability was greater than 0.9, i.e., higher than the value reported by MMAS-Urdu.[83]
	Morisky Medication Adherence Scale (MMAS) or MMAS-8	• One of the most used adherence measurement tools • A validated, structured 8-item self-report measure of medication taking behavior. • Items in the scale address barriers to medication-taking and permit the health care provider to reinforce positive adherence behaviors. • Developed initially for low income, minority patients with hypertension,[84] it	• Five-item-reported MMAS with responses on Likert scale was found to be reliable for estimation of adherence to malaria therapy in endemic areas.[85] • A systematic review by Moon et al (2017) found that while the MMAS-8 tool had acceptable internal consistency and reproducibility in a few diseases like type 2 diabetes.[87] • However, while Morisky recommended a cut-off value of 6, Moon et al report that a higher cut-off

		has also been applied for a range of diseases including malaria.[85,86]	value of 7 or 8 could increase the sensitivity of the tool, albeit with a potential decrease in specificity.[87]
	Pill counts	• Manual & direct – during follow up visits at the health facility and/or home visit with patients asked to present the empty pill box or empty blister packs. • The number of doses remaining in a medication container (e.g., blister pack) are counted, and a comparison is made of how many doses are supposed to remain versus how many remain. • Unannounced pill counts - via phone or through home visits • Electronic monitoring - considered as reference standard of indirect adherence measures. These record the opening of the pill box or blisters packs through an electronic microchip, the underlying assumption being that bottle opening represents medication intake.	• Potential bias is likely as patients are aware of being assessed.[78] • Electronic monitoring may be less prone to recall and social desirability bias, however it can be expensive and relies on good phone networks.[78,88]
	Directly Observed Therapy	• DOT is a process in which a health-care provider directly monitors every dose of patients treatment. • Gold-standard of adherence monitoring, DOT ensures administration of prescribed therapy for the benefit of community disease control and provides a regular venue for detecting adverse effects,	• Although a meta-analysis of randomized clinical trials on directly observed therapy (DOT) has shown no significant impact of DOT on treatment outcomes, historical case series suggest that programmatic implementation is associated with increased treatment completion and decreased drug resistance in communities.[89] • Gold standard? Searching literature

		assessing response to therapy, and encouraging perseverance with drug regimens that are typically difficult to tolerate. • A staff member observes a patient taking a medication, either in person or remotely by video.	
	Ingestible electronic pills/sensors	• Patients ingest a pill or wear a device that passively or actively transmits a signal to an electronic device near or on the body (e.g., patch, breathing tube, wrist-worn device) to track whether a medication was taken	• The current evidence concerning electronic pills or digital pills is not robust. [90] • Ethical concerns of violating individual autonomy, unpleasant form of surveillance, coercion etc. [90]
Outcome oriented measures	Pharmacologic metrics	*Drug concentrations* • Pharmacologic metrics of adherence involve measuring drug concentrations (e.g. Primaquine and carboxyprimaquine) in a biomatrix – most commonly for malaria - in either whole blood or dried blood spots (DBS).[91,92]	• It can be affected by the drug metabolism, gastrointestinal absorption, interaction with other drugs etc. • A combination of structured questionnaire and drug concentration can eliminate all bias subjected to structured questionnaire.[93]
		Methemoglobin (Met-Hb) concentrations • Met-Hb concentrations are elevated following PQ administration since the drug induces oxidative stress on red blood cells resulting in oxidization of the ferrous iron in the haem group.	• This needs more validation as a measure of adherence since Met-Hb concentration may be elevated due to other reasons besides PQ administration.[78]

Annex 2: MMAS-8 Items

- Do you sometimes forget to take your high blood pressure pills?
- Over the past 2 weeks, were there any days when you did not take your high blood pressure medicine?
- Have you ever cut back or stopped taking your medication without telling your doctor because you felt worse when you took it?
- When you travel or leave home, do you sometimes forget to bring along your medications?
- Did you take your high blood pressure medicine yesterday?
- When you feel like your blood pressure is under control, do you sometimes stop taking your medicine?
- Taking medication every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your blood pressure treatment plan?
- How often do you have difficulty remembering to take all your blood pressure medication?

Annex 3: MMAS-5 items

1. Do you ever forget to take your pills?
2. Are you ever careless in taking your pills?
3. Do you ever miss taking your pills when you are feeling better?
4. Do you ever miss taking any of your pills because you are feeling sick?
5. Do you replicate the dose when you are feeling sick?

Annex 4: MARS-5 items

1. I take less than instructed
2. I stop taking it for a while
3. I miss out a dose
4. I alter the dose
5. I forget to take it

Five-point Likert scale (5 = never, 4 = rarely, 3 = sometimes, 2 = often, 1 = very often), with higher scores indicating higher reported adherence.

Annex 5: GMAS constructs and items

Constructs	Items
1. Non-adherence due to patient's behavior, i.e., unintentional and intentional non-adherence	1. Do you have difficulty in remembering to take your medications? 2. Do you forget to take your medication due to your busy schedule, travelling, meeting, events at home, party, marriage, religious celebrations, etc.? 3. Do you discontinue your medication when you feel well? 4. Do you stop taking medications when you feel adverse effects such as gastric discomfort, etc.? 5. Do you stop taking medications without informing the doctor?
2. Non-adherence due to additional disease and pill burden	6. Do you discontinue your medicines due to other medicines that you have to take for your additional disease? 7. Do you find it is a hassle to remember your medications due to medication regime complexity? 8. During the last month, had there been any occasion when you missed your medicines due to progression of disease and addition of new medicines? 9. Do you alter medication regimen, dose and frequency by yourself?
3. Cost-related non- adherence	10. Do you discontinue these medications because they are not worth of the money you spent on them? 11. Do you find it difficult to buy your medicines because they are expensive?