Am. J. Trop. Med. Hyg., 103(1), 2020, pp. 415–420
doi:10.4269/ajtmh.19-0890

Case Report: Primaquine Failure for Radical Cure of *Plasmodium vivax* Malaria in Gambella, Ethiopia

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Abstract. Failures of primaquine for the treatment of relapsed *Plasmodium vivax* malaria is a serious challenge to malaria elimination in Ethiopia, where *P. vivax* accounts for up to 40% of malaria infections. We report here occurrence of a total of 15 episodes of primaquine treatment failure for radical cure in three historical *P. vivax* malaria patients from Gambella, Ethiopia, during 8–16 months of follow-up in 1985–1987. The total primaquine doses received were 17.5 mg/kg, 25.8 mg/kg, and 35.8 mg/kg, respectively. These total doses are much higher than in previous reports of patients with treatment failure in Ethiopia and East Africa. The possibility of new infection was excluded for these cases as the treatment and follow-up were carried out in Addis Ababa, a malaria-free city. Recrudescences were unlikely, considering the short duration pattern of the recurrences. The cytochrome P450 2D6 (CYP2D6) status for these patients is unknown, but polymorphisms have been described in Ethiopia and may have contributed to primaquine treatment failures. It is suggested that further studies be carried out in Ethiopia to determine the prevalence and distribution of primaquine treatment failures in different ethnic groups, considering the impact of CYP2D6 polymorphisms and the potential value of increasing the primaquine dose to avoid relapse.

INTRODUCTION

Approximately 68% of the population of Ethiopia live in areas at risk of malaria infection.[1] According to the health and health-related indicators (2007EC) of the Federal Ministry of Health, malaria is one of the top 10 causes of morbidity and mortality in Ethiopia.[2] Both *Plasmodium falciparum* and *Plasmodium vivax* are co-endemic in Ethiopia. With an estimated 3–5 million cases per year, *P. vivax* accounts for up to 40% of all malaria infections in Ethiopia.[1] *Plasmodium vivax* is characterized by the development of dormant stages of parasites inside hepatic cells, which are called hypnozoites.[3,4] Hypnozoites trigger relapsing episodes of blood-stage infections with different periodicity, for example, the relapses in Southeast Asia are characterized by early and frequent episodes, indicating the need for higher dosing of primaquine therapy.[5,6] The hypnozoite reservoirs present a challenge for malaria control and elimination, as the carriers are asymptomatic.[3,4,7]

Embracing the African Malaria Strategy, the National Malaria Control Program (NMCP) has launched a first phase of elimination program in selected districts.[8] Radical cure of *P. vivax* is critical for the elimination of *P. vivax*, and the country adopted primaquine based on the WHO recommendation of 15 mg base daily for 14 days.[9] However, some studies have shown that the standard WHO-recommended primaquine dose has failed to radically cure *P. vivax* infections in Ethiopia and East Africa.[10,11] Thus, there is a need to establish the primaquine dose that failed to prevent relapse of *P. vivax* infections.

In this case series, we describe three historical cases from the 1980s with a total of 15 episodes of primaquine treatment failure for radical cure. The objective of the case series is to characterize relapsing *P. vivax* infections and document the primaquine dose that failed to prevent relapse of *P. vivax* infections. The specific objectives include the following: to retrospectively analyze data collected from routine healthcare services of three *P. vivax*–infected cases, describe the pattern of relapse characteristics of *P. vivax*, determine the dose of primaquine associated with relapse of *P. vivax*, understand the clinical and hematological effects associated with the use of primaquine for radical cure of *P. vivax* infections, and identify issues that should be considered in future research on effective dose of primaquine for the treatment of relapsing *P. vivax* in Ethiopia. A case series approach was used through compilation, analysis, and synthesis of medical records of the *P. vivax* cases. The medical records including clinical presentation, parasite counts, treatment dates and doses, blood chemistry tests, and outcome of treatment were retrieved and analyzed to achieve the objective of the case series. An official ethical approval to conduct case series analysis was obtained from the Ethiopian Public Health Institute Institutional Review Committee.

STUDY SETTING

Three permanent residents of Addis Ababa, a malaria-free capital city of Ethiopia, located at an altitude 2,355 m (7,726 feet) above sea level, had traveled to Gambella, a malaria-endemic region in western Ethiopia, to provide community service of population resettlement scheme during 1985–1987. The program involved resettlement of people from overcrowded and drought-prone highland areas to underused fertile lowlands such as Gambella. With an average altitude of 300–500 m above sea level and annual rainfall of 120 mm, Gambella is one of the few areas in Ethiopia that have an intense perennial malaria transmission. The three cases had stayed in Gambella malaria-endemic area for 2–11 months before they returned to Addis Ababa. The cases presented with fever at the National Malaria Laboratory Center, Ministry of Health, Addis Ababa, 4–49 days after their return to Addis Ababa. The center was set up by the Ministry of Health to provide free malaria diagnostic and treatment services to self-reporting patients. They were diagnosed with *P. vivax* mono-infection parasites and treated with standard dose of chloroquine followed by primaquine therapy. The cases were followed up from 8 to 16 months at the Malaria Laboratory

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Center in Addis Ababa, outside a transmission area, which provided an opportunity to document the pattern of relapse characteristics of *P. vivax* malaria.

CASE PRESENTATION

We report here clinical records of three Addis Ababa residents, designated as case 1, 2, and 3, who had stayed in Gambella malaria-endemic area for 11, 2, and 3 months, respectively, before they returned to Addis Ababa. The three cases who reported that they were not ill during their stay in Gambella self-reported at the National Malaria Laboratory Center in Addis Ababa with fever between 1985 and 1986 seeking diagnosis and treatment services that are provided for free. Giemsa-stained blood smear examination of the cases revealed the presence of *P. vivax* mono-infection parasites. Details of the three cases are as follows.

Case 1 was a 38-year-old man weighing 64 kg who had stayed in Ubala, Gambella, for 11 months from October 1985 to August 1986. He was on regular weekly 300 mg base chloroquine prophylaxis only for the first 8 months of his 11-month stay in Gambella (Figure 1). He returned to Addis Ababa in September 1986 and reported with symptoms suggestive of malaria 49 days after his return to Addis Ababa. Case 1 experienced four relapsing attacks during an 8-month follow-up (Table 1). The first three relapses were of short interval with an average of 28 days and a range of 26–32 days, whereas the fourth relapse occurred at a 121-day interval.

Case 2 was a 34-year-old man weighing 60 kg who had stayed in Ubala, Gambella, for 2 months from July 1985 to August 1985. He was on regular weekly 300 mg base chloroquine prophylaxis before his departure for Gambella, during his 2-month stay in Gambella, and for additional 4 weeks (September 1985) after his return to Addis Ababa in August 1985 (Figure 1). He reported with symptoms suggestive of malaria 47 days after his return to Addis Ababa and 22 days after his last chemoprophylaxis dose. Case 2 experienced five relapsing attacks during the 9-month follow-up (Table 2). The intervals of the four relapses were of short duration with an average interval of 26 days and a range of 27–40 days. The fifth relapse occurred after an interval of 63 days.

Case 3 was a 52-year-old man weighing 52 kg who had stayed in Keto-Shebelle, Gambella, for 3 months (June 1986–August 1986) but did not take any malaria chemoprophylaxis for this trip. He returned to Addis Ababa at the end of August 1986 and reported with symptoms suggestive of malaria 4 days after his return to Addis Ababa (Figure 1). Case 3 had six relapsing attacks during 16 months of follow-up. The first four relapses occurred at an interval of 37 days and a range of 29–47 days, whereas the fifth and sixth relapses occurred at an interval of 99 days and 154 days, respectively (Table 3). Overall, 11 of the total 15 relapse attacks of the three cases had a short interval of about 1-month duration and the other four relapses occurred at an interval of 2 months to 5.1 months (Figure 1).

TREATMENT AND OUTCOME

The first attacks of each of the three cases were treated with a standard dose of 1,500 mg base chloroquine over 3 days followed by a low-dose primaquine therapy of 15 mg per day for 5 days based on national guidelines. Until a few years ago, the general practice of malaria control program in Ethiopia involved the use of 5-day primaquine therapy to treat *P. vivax* cases among permanent residents of endemic areas and mobile populations. The 5-day primaquine regimen for *P. vivax* malaria treatment protocol was also intended to target *P. falciparum* gametocytes, as the prevalence of *P. falciparum* and *P. vivax* mixed infections is very high in Ethiopia. Radical treatment was provided to those who live in malaria-free areas if they agree to comply with the 14-day primaquine treatment regimen. After the first attacks were managed, the three cases reported back to the same malaria center with complaints of malarial illness for a number of times with different intervals.

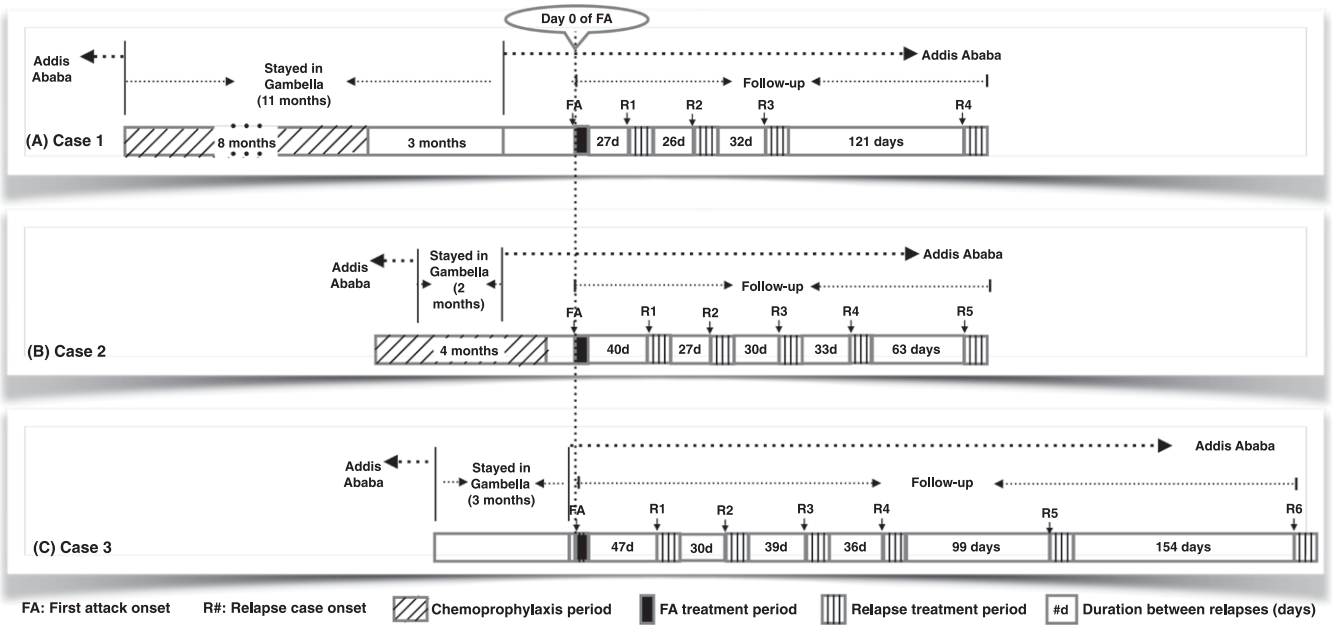

FIGURE 1. Timing of chloroquine prophylaxis, onset of primary and relapse attacks including treatment periods, interval between relapses, and time of travel to and from Gambella of the three cases, 1985–1987, Ethiopia.

TABLE 1

Malaria attack characteristics, drug dosage, and outcome of treatment for case 1 (body weight = 64 kg), October 1986–July 1987, Ethiopia

Date of diagnosis	*Plasmodium vivax* parasite count/mm^3 of blood	Date of chloroquine treatment (1,500 mg over 3 days)	Primaquine			Duration of relapse (days)
			Treatment provided	Dose (mg/kg of body weight)	Date of completion of treatment	
October 29, 1986	–	October 29–31, 1986	15 mg/day for 5 days	1.2	November 4, 1986	First attack
December 2, 1986	1,800 on d0, 120 on d1, and negative on d2	December 2–4, 1986	15 mg/day for 14 days	3.3	December 1, 1986	27
January 12, 1987	4,400 on d0, 2960 on d1, and negative on d2	January 12–14, 1987	30 mg/day for 14 days	6.6	January 27, 1987	26
February 27, 1987	6,000 on d0, 120 on d1, and negative on d2	February 27–29, 1987	30 mg/day for 14 days	6.6	March 14, 1987	32
July 14, 1987	9,110 on d0, 120 on d1, and negative on d2	July 14–16, 1987	Opted out of treatment	–	–	121
Total primaquine dose over the follow-up period				17.6	–	–

TABLE 2

Malaria attack characteristics, drug dosage, and outcome of treatment for case 2 (body weight = 60 kg), October 1985–July 1986, Ethiopia

Date of diagnosis	*Plasmodium vivax* parasite count/mm^3 of blood	Date of chloroquine treatment (1,500 mg over 3 days)	Primaquine			Duration of relapse (days)
			Treatment provided	Dose (mg/kg of body weight)	Date of completion of treatment	
October 17, 1985	–	October 17–19, 1985	15 mg/day for 5 days	1.3	October 23, 1985	First attack
December 2, 1985	8,640 on d0	December 2–4, 1985	15 mg/day for 14 days	3.5	December 17, 1985	40
January 13, 1986	4,230 on d0	January 13–15, 1986	30 mg/day for 14 days	7.0	January 28, 1986	27
February 27, 1986	4,000 d0	March 27–1, 1986	30 mg/day for 14 days	7.0	March 13, 1986	30
April 15, 1986	12,800 d0	April 15–17, 1986	30 mg/day for 14 days	7.0	May 6, 1986	33
July 9, 1986	320 d0	July 9–11, 1986	Did not take primaquine	–	–	63
Total primaquine dose over the follow-up period				25.8	–	–

TABLE 3
Malaria attack characteristics, drug dosage, and outcome of treatment for case 3 (body weight = 52 kg), August 1986–October 1987, Ethiopia

Date of diagnosis	*Plasmodium vivax* parasite count/mm^3 of blood	Date of chloroquine treatment (1,500 mg over 3 days)	Primaquine		Date of completion of treatment	Duration of relapse (days)
			Primaquine treatment provided	Total dose (mg/kg of body weight)		
August 25, 1986	–	Augut 25–27, 1986	15 mg/day for 5 days	1.4	September 1, 1986	First attack
October 18, 1986	900 on d0, 220 on d1, and negative on d2	October 18–20, 1986	15 mg/day for 14 days	4.0	November 3, 1986	47
December 01, 1986	14,640 on d0, 280 on d1, 60 on d2, and negative on d3	December 01–3, 1986	22.5 mg/day for 14 days	6.1	December 16, 1986	29
January 23,1987	180 on d0, 520 on d1, and negative on d2	January 23–25, 1987	30 mg/day for 14 days	8.1	February8, 1987	39
March 16, 1987	18,000 on d0, 520 on d1, and negative on d2	March 16–18, 1987	30 mg/day for 14 days	8.1	April 1, 1987	36
July 8, 1987	46,800 on d0, 1,960 on d1, and negative on d2	July 8–10, 1987	30 mg/day for 14 days	8.1	July 24, 1987	99
December 24, 1987	1,640 on d0, 220 on d1, and negative on d2	December 24–26, 1987	Opted out of treatment	–	–	154
Total primaquine dose over the follow-up period				35.8	–	–

Blood smear examinations of the three cases during each visit had revealed the presence of *P. vivax* mono-infection parasites. They confirmed that they did not travel outside Addis Ababa, indicating that the three cases had relapse attacks. Considering that Addis Ababa is free of malaria transmission, the center treated the relapsing infections with chloroquine over 3 days followed by primaquine for 14 days based on WHO recommendations for radical cure as follows.

The first relapsing attack of case 1 was treated with a standard dose of 1,500 mg base chloroquine over 3 days followed by 15 mg base primaquine per day for 14 days. The subsequent two relapsing attacks were treated with a standard dose of 1,500 mg base chloroquine over 3 days followed by 30 mg base primaquine per day for 14 days each. Detailed information on parasite density, chloroquine and primaquine dose administered, and date of treatment completion, onset, and duration between relapses for the relapsing attacks is presented in Table 1. The total primaquine dose administered was 17.6 mg/kg of body weight. Similarly, all relapsing infections of case 2 were initially treated with a standard dose of 1,500 mg base chloroquine over 3 days. Following the chloroquine treatment, the first relapsing attack was treated with 15 mg base primaquine per day for 14 days. The subsequent three relapsing infections were treated with 30 mg base per day for 14 days after completing their respective chloroquine regimens (Table 2). The total primaquine dose administered was 25.8 mg/kg of body weight. Relapsing infections of case 3 were also initially treated with a standard dose of 1,500 mg base chloroquine over 3 days. Following the chloroquine treatment, the first two relapsing attacks were treated with 15 mg base primaquine per day and 22.5 mg base primaquine per day, respectively, each for 14 days. Each of the subsequent three relapses was treated with 30 mg base primaquine per day for 14 days following the completion of the chloroquine regime (Table 3). Total primaquine dose administered was 35.8 mg/kg of body weight. The chloroquine treatment was efficacious as the asexual malaria parasites were cleared by day 2 in all first and relapsing infections, although *P. falciparum* resistance to chloroquine had been recorded more than three decades ago in Ethiopia.[12]

The patients were required to take their daily primaquine treatment doses at the Malaria Diagnostic Center under the supervision of laboratory personnel except for weekends when the drug was given to the patients with instruction to use them at home. Compliance for the self-treatment on weekends was ascertained by interview of the patients on following weekdays. Because primaquine can cause hemolytic anemia, particularly in those individuals who are deficient for the enzyme glucose-6-phosphate dehydrogenase (G6PD),[13,14] routine testing for G6PD deficiency has to be carried out before initiating primaquine treatment for radical cure of *P. vivax* patients. However, because of lack of its availability, the three cases were not screened for G6PD deficiency. To ensure the safety of the patients, each patient taking repeated doses of primaquine was required to take hematology and clinical chemistry test at the National Research Institute of Health, which is now renamed as Ethiopian Public Health Institute. The treatments were well tolerated except for few complaints. Cases 1 and 2 had complained of abdominal cramp and tiredness, but each took their dosages and continued the follow-up for 8 and 9 months, respectively. Hematology and clinical chemistry test results of serum glutamic oxaloacetic transaminase, serum

glutamic pyruvic transaminase, bilirubin, creatinine, albumin, protein, hemoglobin, and hematocrit for the three cases are summarized in Table 4. Case 3, who experienced an elevated direct and total bilirubin levels (0.85 mg% and 2.88 mg %, respectively) and low hematocrit level (39.1), opted out after 16 months of follow-up.

DISCUSSION

The *P. vivax* malaria strains of the three cases were acquired in Gambella, Ethiopia, and managed for the first attack as well as relapses in a non-malarious setting in Addis Ababa, Ethiopia. The total doses of primaquine administered to cases 1, 2, and 3 were 17.6 mg/kg, 25.8 mg/kg, and 35.8 mg/kg, respectively, but failed to radically clear the parasites. The primaquine doses that failed to radically cure *P. vivax* infections from Gambella are much higher than doses previously reported with primaquine treatment failures for Ethiopia and East Africa[10,11] but appear to fall within the category of primaquine doses recommended for Southeast Asia and Oceania.[9,15] It also appears that the Gambella *P. vivax* malaria strain shows similar characteristics to *P. vivax* malaria from Southeast Asia in terms of early and frequent relapses and requirement for higher dosing of primaquine therapy.[5,6] Because of multiple reports of primaquine failure for radical cure of *P. vivax* infections from various regions, the WHO recommends a primaquine dose of 15 mg base daily for 14 days for all regions except for Southeast Asian region, which is recommended a dose of 30 mg daily for 14 days.[9] Nevertheless, the Centers for Disease Control (CDC) recommended use of 30 mg daily for 14 days for all regions.[16] The three cases from Ethiopia support other reports indicating failure of *P. vivax* malaria to respond to standard doses of primaquine in East Africa.[17,18] A study on Israel tourists infected with *P. vivax* strain from Ethiopia contracted mostly from around the Omo River Valley showed that a primaquine dose > 3.5 mg/kg was effective in relapse prevention; however, the authors did not indicate the end point of the effective dose for radical cure.[10]

The contribution of polymorphisms in the human cytochrome P450 2D6 (CYP2D6) in explaining the findings can not be ruled out as its role in metabolizing primaquine to its redox-active metabolite and its association with primaquine failure is well documented.[19–21] Although information relating to CYP2D activity in mediating primaquine metabolism for these three cases is not available, a study on the effect of CYP2D6 activity on the metabolism of debrisoquine among healthy Ethiopian population showed that 29% of the study participants carried duplicated and multiduplicated genes indicating ultrarapid metabolizers.[22]

Primaquine failure for radical cure of *P. vivax* malaria is a challenge to malaria control and elimination. The Ethiopian NMCP had developed a strategic plan for malaria elimination and updated its policy on primaquine use for radical treatment of *P. vivax* in selected districts targeted for malaria elimination and for those *P. vivax* patients who live outside malaria-endemic areas. The information generated from the three cases relating to primaquine failure and characteristics of the relapsing episodes is of relevance to NMCP.[13] The high-dose primaquine treatments were well tolerated except for few complaints and one case of elevated bilirubin level and low hematocrit level, indicating that the three cases were most probably not G6PD deficient. The total primaquine doses for cases 1 and 2 are in line with a previous observation that daily doses of 0.5 mg/kg for 50 weeks were well tolerated[20] The prevalence of G6PD deficiency and its distribution in Ethiopia is not well known.[23–25] Studies conducted in different settings in Ethiopia had indicated a low prevalence of G6PD deficiency in most parts of the country with pockets of higher prevalence in areas such as Gambella among the Nuer/Anuak population.[23–25] The nation-wide study conducted by Assefa indicated the absence of the common G6PD-deficient African and Mediterranean variants.[23]

The case series analysis has some limitations. Primarily, the data are old, and thus, the efficacy of the drug may have changed over the years to reflect the current situation. However, primaquine has rarely been used for radical treatment in endemic areas of the country. In the absence of primaquine pressure for decades in the Ethiopian setting, it is unlikely that the efficacy of the drug as anti-relapse therapy of *P. vivax* has changed over time. Second, the data are based on the clinical records of patients who sought diagnosis and treatment as part of routine healthcare services and was not part of research-based investigation. Although this may affect the quality of the data, the procedure in service delivery and documentation of information that was followed ensured the availability of detailed and complete information on clinical presentation, treatment, and outcome. Because the case series is based on few cases from one site, the findings cannot be generalized and should be supported with other studies covering different geographic areas. Finally, future primaquine efficacy assessments for radical cure of *P. vivax* need to consider the role of CYP2D6 enzyme activity on the metabolism of primaquine to its active metabolites.

TABLE 4

Hematology and clinical chemistry test results of the three *Plasmodium vivax* cases by the series of relapse attacks, National Public Health Institute of Ethiopia, 1986–1987

	Date of laboratory testing (timing in relation to relapse attach series)						
	Case 1		Case 2		Case 3		
Type of laboratory tests	January 15, 1987 (relapse 2)	March 20, 1987 (relapse 3)	January 4, 1986 (relapse 2)	May 10, 1986 (relapse 4)	December 6, 1986 (relapse 2)	July 13, 1987 (relapse 4)	December 27, 1987 (relapse 6)
SGOT (IU/L)	17	21	15	21	26	22	26
SGPT (IU/L)	35	33	23	35	24	22	32
Bilirubin direct (mg/dL)	0.12	0.51	0.03	0.24	0.40	0.45	0.85*
Bilirubin total (mg/dL)	0.82	1.52	0.62	0.49	1.40	1.41	2.88*
Creatinine (mg/dL)	1.1	0.9	1.0	1.5	1.4	1.0	1.4
Protein (mg/dL)	7.1	6.5	7.9	–	6.9	5.8	7.9
Albumin (mg/dL)	3.8	5.0	4.2	4.5	3.8	–	4.0
Hemoglobin (gm)	14.2	13.1	17	17	15.3	13.4	14
Hematocrit (%)	42	39	51	52	45	–	39.1*

* Abnormal test results.

CONCLUSION

Primaquine failure for the radical cure of *P. vivax* malaria in Ethiopia is a challenge to malaria control and elimination in the country. The high-dose primaquine failure for treatment of the three patients observed during 8–16 months of follow-up is a concern that would demand systematic studies. Cytochrome P-450 2D6 is involved in the metabolism of primaquine to its active metabolite against hypnozoites, and it is important to identify the association between CYP2D6 activity and primaquine failure in different settings in Ethiopia. It will be prudent to consider adjusting the standard treatment dose of primaquine for radical cure to daily 0.5 mg/kg for 14 days in-line with the CDC recommendation and the WHO guideline issued for Southeast Asia. Despite the high primaquine treatment regimen, the treatments were well tolerated. In view of the requirement for high primaquine dosing, *P. vivax* patients need to be tested for G6PD deficiency before initiating treatment with primaquine. As this case series is limited to Gambella region only, additional study in different geographical areas of the country is suggested to determine the prevalence and distribution of primaquine treatment failures to come up with appropriate national drug policy. Compliance on the use of 14-day primaquine regimen is a challenge for malaria elimination in Ethiopia. It has been reported that use of a single dose of 300–600 mg base of tafenoquine and chloroquine combination is as efficacious as primaquine 15 mg/kg/day for 14 days for preventing relapse of *P. vivax*.[26] We recommend that such combination be evaluated in an Ethiopian setting.

Received December 2, 2019. Accepted for publication April 6, 2020.

Published online May 11, 2020.

Acknowledgments: We gratefully acknowledge the input of professionals who provided expert opinion in undertaking the case report. We would like to thank the National Malaria Laboratory Center, Addis Ababa, for availing the records of the cases.

Financial support: A. T. and H. D. T. were supported by CNHDE. Saint Paulos Hospital, Millennium Collage, and National Research Institute of Health supported A. G. and A. W., respectively.

Disclaimer: The funders had no role in the study design, data analysis, data interpretation, or writing of the manuscript.

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