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An observational pilot study of an active surveillance tool to enhance pharmacovigilance in Brazil

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Abstract

Background Active surveillance involves systematically monitoring patients to seek detailed information about the occurrence of adverse events (AEs) following drug administration. The Seta technology was developed to improve active surveillance of AEs or pregnancy in low- and middle-income countries and geographically challenging areas. Seta actively solicits responses from participants via WhatsApp messages. The study aimed to determine whether Seta facilitated reporting of AEs and pregnancies to the Brazilian National Health Surveillance Agency (ANVISA).

Methods Malaria patients participating in the Tafenoquine Roll-out STudy (TRuST) in Brazil's Amazon region were invited to participate in this observational pilot study evaluating Seta. The study was conducted at two sites from 27 July 2022 to 28 October 2022. Seta sent messages to all participants on Day 7 and in Week 8 asking if they had experienced an AE or if they had become pregnant during the time since they took the malaria medication. If a participant responded "yes", a pharmacovigilance coordinator (PVC) called them to collect further details, which the PVC was then encouraged to report to ANVISA.

Results This pilot study included 149 participants, 50 from Manaus and 99 from Porto Velho. On Day 7, 117 (79%) of 149 participants responded to WhatsApp messages generated by Seta asking whether they had experienced an AE or become pregnant; 45 participants responded "yes". At Week 8, 64 (55%) of the Day 7 responders also responded, 10 of whom indicated that they had experienced an AE or become pregnant. A total of 55 follow-up calls were therefore attempted by PVCs, of which, 25 (45%) were answered and allowed for reporting of AEs and pregnancies, as appropriate, to ANVISA.

Conclusions This observational pilot study provides insights into how digital reporting tools such as Seta can enhance pharmacovigilance in remote areas and build upon existing signal detection methodologies. Twenty-five AEs or pregnancies were reported to ANVISA that were unlikely to have been reported otherwise.

Keywords Active surveillance, Adverse event, Brazil, Malaria, Pharmacovigilance, Tafenoquine, Technology, WhatsApp

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Background

An increasing number of medicines are being developed to address diseases that are prevalent only, or mainly, in low- and middle-income countries [1, 2]. However, these countries' health surveillance systems (including pharmacovigilance (PV)) have not kept pace with such innovations and need strengthening [1, 2]. Even if countries have health infrastructure in place for safety reporting, healthcare professionals may not use the relevant systems well, and the collection and analysis of safety data can be limited. Therefore, new approaches are required to effectively monitor the introduction of new medicines and health technologies in low-resource and geographically challenging settings [1–3].

Spontaneous safety reporting is the most widely used form of PV; however, this is often not well-established in low-resource settings. The World Health Organization promotes a method of active surveillance known as cohort event monitoring, in which data are collected for all adverse events (AEs) among a patient cohort of predefined size [4, 5]. Active surveillance, also termed active PV, involves systematically monitoring patient encounters to seek information about the presence or absence of AEs on an ongoing basis within a defined group of patients. Active surveillance has proved an effective way to monitor the safety of treatments for, among other infections, human immunodeficiency virus (HIV) and *Plasmodium falciparum* infections in Africa [6–8].

In Brazil, the reporting of AEs remains suboptimal [9, 10]; hence, in 2018, the Brazilian National Health Surveillance Agency (ANVISA) introduced an initiative to improve the national PV system [10] and comply with international PV standards [4]. Active surveillance has since been deployed very effectively in Brazil, including when dolutegravir (DTG) was introduced for the treatment of HIV. Patients returning to a pharmacy for their second prescription of DTG were asked to complete a safety questionnaire. More than 70,000 patients participated, representing approximately 90% of those receiving DTG treatment [11]. However, this type of approach is less likely to work for patients who take medications that do not require subsequent visits to a pharmacy or health facility or who live in remote areas.

Seta is a new technology, designed for GSK by the digital communication company medDigital (medDigital Ltd, London, UK), to facilitate active surveillance. Seta is a web application available through a monthly subscription and is accessible through any device able to browse the internet. Seta relies on the widely used mobile messaging tool WhatsApp (WhatsApp LLC) to solicit health information from individuals. A pilot implementation project was performed concurrently with the Tafenoquine Roll-out STudy (TRuST) in Brazil (NCT05096702) to determine whether Seta could enhance PV. In the TRuST study, patients in the Amazon region who had *Plasmodium vivax* malaria were enrolled and treated with a single dose of tafenoquine [12, 13]. Tafenoquine (Kozenis; GSK) was developed by GSK and Medicines for Malaria Venture for the treatment of malaria. In 2018, tafenoquine was approved for use by the United States Food and Drug Administration [14] and the Australian Therapeutic Goods Administration [15]. It received its first market approval in an endemic country from ANVISA in 2019 [16], followed by approval in other countries.

In this pilot study, the primary objective was to assess whether Seta could facilitate the reporting of AEs and pregnancies by patients enrolled in the TRuST study to ANVISA via the VigiMed system. The secondary objective was to establish the technology's sustainability. This was defined as the proportion of participants who responded to messages soliciting health information for each month of recruitment.

Methods

Study design and sites

This observational, non-interventional, pilot study was conducted at two sites in the Amazon region of Brazil (Fundação de Medicina Tropical Dr Heitor Vieira Dourado located in Manaus, Amazonas, and Centro de Pesquisa em Medicina Tropical de Rondônia located in Porto Velho, Rondônia; protocol number 213047).

Seta technology

The Seta technology was designed by medDigital (www.meddigital.com) to facilitate active surveillance of medicines in low-resource or geographically challenging settings; its use has been approved by the Brazilian Research Ethics Committee. The Seta technology is a bespoke, internet-based application that was designed to integrate a patient-facing website that provides information about a study with an administrative portal. The Seta technology uses an application programming interface to connect with the WhatsApp Business Platform to send messages to and receive messages from patients using the WhatsApp mobile application on compatible Android or iOS devices.

The Seta's administrative portal is accessible by PV coordinators (PVCs) to check patients' responses and identify those who had experienced an AE following drug exposure or had become pregnant in the period following drug exposure. If a patient reports issues with their treatment by WhatsApp or phone call to the PVC that the PVC feels may warrant medical attention, the PVC may contact the patient and advise them to access medical care through their routine health care system.

Enrollment of patients

Patients enrolled in TRuST were invited to participate in this pilot study via self-enrollment using WhatsApp or by a PVC, using Seta. The PVCs were registered nurses with relevant experience working at one of the two clinics, with medical oversight. Two PVCs were involved, one per clinic.

All potential participants received an explanation of the study and were provided with an information sheet. The recruitment period was from 27 July 2022 to 31 August 2022, the study was conducted from 27 July 2022 to 28 October 2022. Inclusion criteria were: ≥ 18 years of age, participating in TRuST, receiving malaria treatment, having access to a smartphone, having WhatsApp downloaded on their smartphone, and being familiar with the use of WhatsApp. Patients agreeing to participate in the study were asked to consent to receive WhatsApp notifications and phone calls from a PVC, if necessary, and for their personal information (name, date of birth, and smartphone number) to be stored in a secure database. Seta generated two WhatsApp messages upon completion of enrollment to inform the patient that they had successfully enrolled and to provide a link to the pilot study's website, which included further information and a privacy notice. Participants were told they could withdraw from the study at any time and for whatever reason by sending a WhatsApp message saying "WITHDRAW".

Data collection procedure and variables

Seta was programmed to send messages to all participants on Day 7 and in Week 8 after they had received the malaria medication, asking if they had experienced an AE after taking malaria medication or if they had become pregnant during the time since they took malaria medication. Participants could respond either "yes" or "no". Participants who did not respond to either the Day 7 or Week 8 messages within 72 h were considered lost to follow-up (LTFU). Patients LTFU at Day 7 were not recontacted at Week 8. The WhatsApp messages also advised the participants to contact their usual clinic if they were unwell. Seta was not used to make clinical management decisions.

If a participant responded "yes", Seta sent a message (via email) to a PVC, instructing them to call the participant to collect details of the AE or pregnancy. Participants who failed to respond to a follow-up phone call from a PVC on two occasions were designated as LTFU. PVCs were encouraged to report any AE or pregnancy to ANVISA via VigiMed [17]. In the case of any AEs involving tafenoquine, the PVC was also encouraged to send an anonymized copy of the VigiMed report to GSK (reports for AEs were sent within five calendar days and within one working day for serious AEs). To avoid duplicate reporting, GSK did not notify ANVISA of any AEs arising from the study. A participant flow diagram is shown in Fig. 1.

Outcomes

To assess the effectiveness of Seta as a resource for enhancing PV two outcomes were used: (i) The proportion of participants who responded to WhatsApp messages soliciting health information, and (ii) the number of VigiMed reports submitted to ANVISA. The outcome to assess the technology's sustainability during the study period was the proportion of participants who responded to WhatsApp messages soliciting health information for each month of recruitment over time.

Data management and analysis

The application was written in Hypertext Markup Language. Patient data were stored in the UK with Amazon Web Services' secure Elastic Compute Cloud, complying with the required standards in the UK and Brazil for data protection of personally identifiable information and health data. The data were exported from the web-based application and analysed by medDigital staff using Microsoft Excel on personal desktop computers. For the efficacy endpoints, the proportion (%) was calculated using n/N*100%, with n indicating the number of patients giving a specific answer and N the number of patients at the specific location. The corresponding 95% confidence interval (CI) was determined with the formulas: $CI_{min} = \%-(1.96*(\sqrt{(\%*(100-\%)/N)}))$ and $CI_{max} = \% + (1.96*(\sqrt{(\%*(100-\%)/N)}))$.

Results

Participants

In total, 154 individuals enrolled in the study: 50 at the Manaus site and 104 at the Porto Velho site (Table 1). Most participants from Manaus (96%, n = 48/50) and all participants from Porto Velho (100%, n = 104/104) were enrolled by the PVCs. Five enrolled participants (3.2%) were excluded from the study as they had provided invalid phone numbers. So, a total of 149 participants were included in the analysis.

Of the participants in the analysis set, 32 of 149 did not respond on Day 7, and 53 of the remaining 117 did not respond in Week 8. So, in total, 57% (n = 85/149) were considered LTFU as they did not respond to messages within 72 h. The 85 LTFU participants comprised 34 participants from Manaus (68%) and 51 from Porto Velho (52%). No participants requested to withdraw from the study (Table 1).

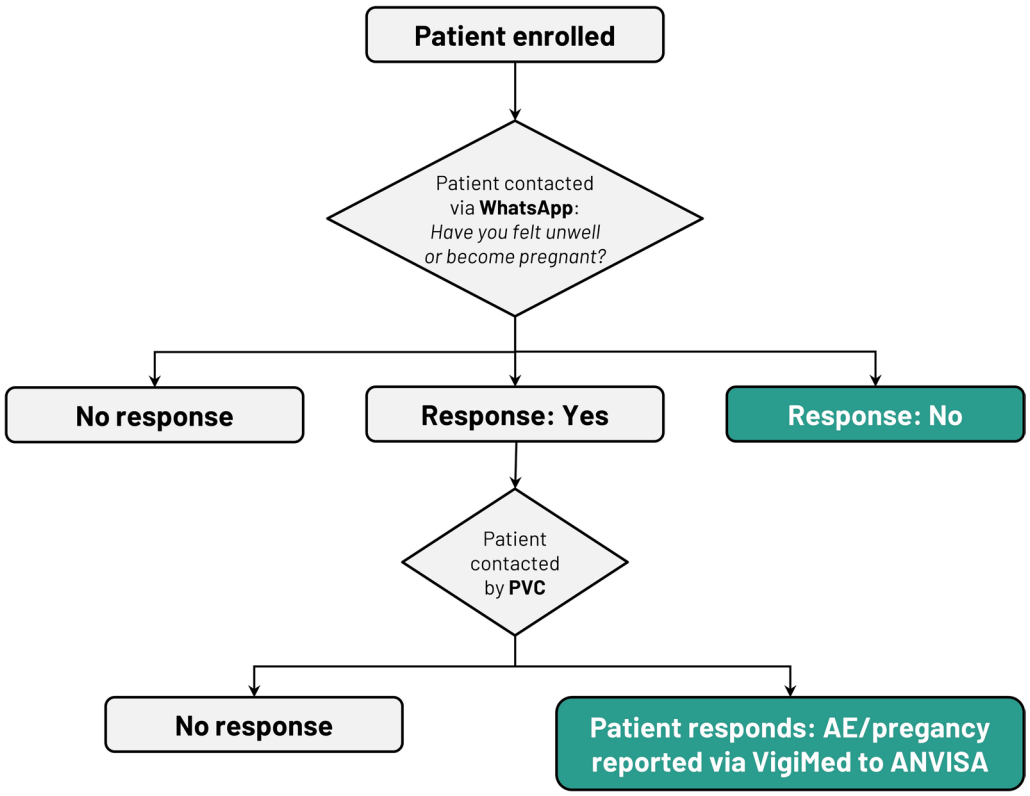

Fig. 1 Participant flow diagram. WhatsApp messages were sent on Day 7 and in Week 8. The same process applied at both time points. The green boxes denote outcomes that demonstrate the effectiveness of the Seta technology. *AE* adverse event, *ANVISA* National Health Surveillance Agency, *PVC* pharmacovigilance coordinator

Table 1 Participant enrollment for the Manaus and Porto Velho study sites

	Manaus enrolled, n (%)	Porto Velho enrolled, n (%)	Total enrolled, n (%)
Enrolled set (N = 154)			
Total enrolled	50 (100%)	104 (100%)	154 (100%)
Self-enrolled	2 (4%)	0 (0%)	2 (1%)
PVC-enrolled	48 (96%)	104 (100%)	152 (99%)
Removed from study*	0 (0%)	5 (5%)	5 (3%)
Analysis set (N = 149)			
Total participants	50 (100%)	99 (100%)	149 (100%)
Withdrawal	0 (0%)	0 (0%)	0 (0%)
LTFU	34 (68%)	51 (52%)	85 (57%)

LTFU lost to follow-up, *N* total number in set, *n* number per category, *PVC* pharmacovigilance coordinator

* Participants removed from the study due to having provided invalid phone numbers

Outcomes to assess the effectiveness of the Seta technology

The primary outcome used to assess the effectiveness of the Seta technology was the proportion of participants who answered WhatsApp messages. All 149 participants received a WhatsApp message on Day 7 and the 117 participants who responded on Day 7 received a message in Week 8.

On Day 7, 79% (n = 117/149) of all participants responded, with 30% (n = 45/149) responding "yes", signaling a potential AE or pregnancy, and 48% (n = 72/149) responding "no" (Table 2). At Week 8, 55% (n = 64/117) of the remaining participants responded, with 9% (n = 10/117) responding "yes" and 46% (n = 54/117) responding "no" (Table 3).

The secondary outcome used to assess the effectiveness of the Seta technology was the number of VigiMed reports submitted to ANVISA. Following the 55 "yes" responses to the WhatsApp message on Day 7 and Week 8, PVCs were able to make contact and report a potential AE or pregnancy via VigiMed to ANVISA in 45% (25/55) of cases. For the remaining 55% (n = 30/55)

Table 2 Primary and secondary efficacy endpoints for Day 7

	Manaus N = 50 n, % (95% CI)	Porto Velho N = 99 n, % (95% CI)	Total N = 149 n, % (95% CI)
Participants responding "yes"	14, 28% (16–40%)	31, 31% (22–40%)	45, 30% (23–38%)
Participants responding "yes" with at least one AE or pregnancy subsequently reported to ANVISA	3, 6% (– 1–13%)	18, 18% (11–26%)	21, 14% (9–20%)
Participants responding "no"	21, 42% (28–56%)	51, 52% (42–61%)	72, 48% (40–56%)
No response (LTFU)	15, 30% (17–43%)	17, 17% (10–25%)	32, 21% (15–28%)
Composite endpoint*	24, 48% (34–62%)	69, 70% (61–79%)	93, 62% (55–70%)

AE adverse event, *ANVISA* National Health Surveillance Agency, *CI* confidence interval, *LTFU* lost to follow-up, *N* total number in set, *n* number per category

* Participants responding "yes" with at least one AE or pregnancy reported to ANVISA, or responding "no"

Table 3 Primary and secondary efficacy endpoints for Week 8

	Manaus N = 35 n, % (95% CI)	Porto Velho N = 82 n, % (95% CI)	Total N = 117 n, % (95% CI)
Participants responding "yes"	4, 11% (1–22%)	6, 7% (2–13%)	10, 9% (3–14%)
Participants responding "yes" with at least one AE or pregnancy subsequently reported to ANVISA	1, 3% (– 3–8%)	3, 4% (0–8%)	4, 3% (0–7%)
Participants responding "no"	12, 34% (19–50%)	42, 51% (40–62%)	54, 46% (37–55%)
No response (LTFU)	19, 54% (38–71%)	34, 41% (31–52%)	53, 45% (36–54%)
Composite endpoint*	13, 37% (21–53%)	45, 55% (44–66%)	58, 50% (41–59%)

AE adverse event, *ANVISA* National Health Surveillance Agency, CI confidence interval, *LTFU* lost to follow-up, *N* total number in set, *n* number per category

* Participants responding "yes" with at least one AE or pregnancy reported to ANVISA, or responding "no"

of "yes" responses, PVCs' attempts to contact participants were unsuccessful.

The composite endpoint consisted of the availability of a conclusive response from a participant. A response was considered conclusive if a participant responded "no" or sent a "yes" response that led to at least one AE or pregnancy being reported to ANVISA. Conclusive responses were available for 62% (n = 93/149) of participants on Day 7 and 50% (n = 58/117) in Week 8 (Tables 2 and 3).

Outcome to assess the sustainability of the Seta technology

To assess Seta's sustainability, the aim was to analyze the proportion of participants who responded to WhatsApp messages for each month of recruitment over time. However, due to the limited sample size (n = 149), the low response rate in Week 8 of the study (55%, n = 64/117), and the large number of participants that were LTFU at either Day 7 or in Week 8 (57%, n = 85/149), no meaningful analysis of the sustainability could be performed.

Discussion

This pilot study provides insights into how Seta can be used to enhance active surveillance. The data collected by Seta showed that most participants (117/149, 79%) enrolled in this study who responded on Day 7 were able to digitally communicate whether they had experienced an AE or a pregnancy. In addition, the study showed that Seta enabled PVCs to follow up AEs and pregnancies relayed via WhatsApp by participants (21/45, 47% at Day 7; 4/10, 40% at Week 8), allowing these events to be reported to ANVISA via VigiMed reports (the study's primary objective).

The sustainability of Seta over time (the study's secondary objective) could not be determined with this pilot study due to the small sample size, the low response rate in Week 8 of the study, and the large number of participants that were LTFU. The reasons for the large loss to follow-up and the low response rates in Week 8 were not investigated and are, therefore, unknown. However, as tafenoquine was given as a single-dose treatment (on Day

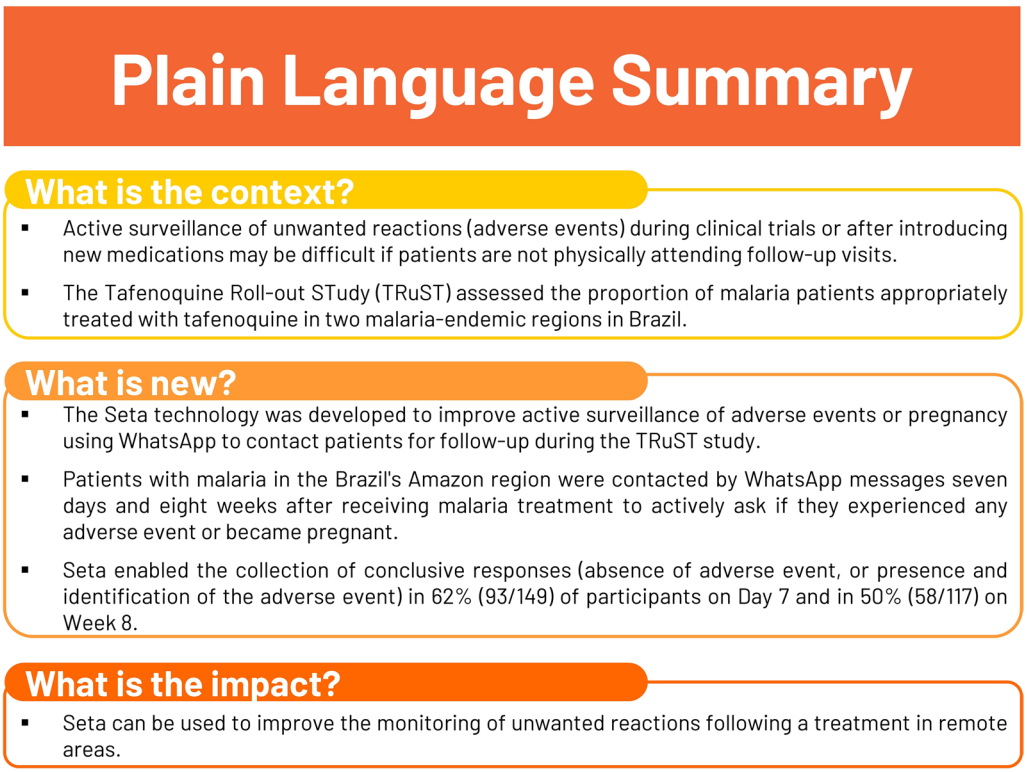

Fig. 2 Plain language summary

0), the participants may have lost interest in the study over time.

In studies involving active surveillance in low- or middle-income countries, the numbers of participants LTFU were much lower; for example, 3.9% of participants were LTFU in a study of treatment for *P. falciparum* malaria in Swaziland, while 18% were LFTU in a study of HIV treatment in Namibia [7, 8]. However, the medications being monitored in those studies required return visits (which would have greatly reduced loss to follow-up), which was not the case for the tafenoquine used in the current pilot study. In various studies in low- and middle-income countries of single-dose treatment regimens to prevent mother-to-child HIV transmission, loss to follow-up varied from 26 to 81% [18–20]. In HIV studies, stigma also plays a role in the loss to follow-up. However, an analysis of socio-demographic factors associated with loss to follow-up in a study to prevent HIV transmission in India found that having less than a graduate-level education (relative risk [RR] = 6.32) and coming from a poor family (RR = 1.61) greatly contributed to the loss to follow-up of HIV-infected pregnant women before delivery [20]. These factors may have also contributed to the loss to follow-up in the current study. In general, there is increasing evidence to support the efficacy of mobile health interventions, such as those used in this pilot study, in improving health outcomes in low- and middle-income countries [21]. However, for single-dose medications, additional incentives may be needed to reduce loss to follow-up.

An important difference between active surveillance of treatments of chronic diseases (such as HIV) versus acute infectious diseases is that adherence to follow-up for acute infectious diseases is affected by the success of the treatment. If the therapeutic outcome is good after a single treatment, the patient is less likely to see the need for follow-up. In contrast, for chronic diseases and more complex clinical conditions, the need for adherence to follow-up will be obvious to the patient.

In a study involving 789 healthcare professionals in Brazil, it was found that 68% of these healthcare professionals under-reported adverse drug reactions [22]. Another study among 761 healthcare professionals in Brazil found that questions to assess knowledge, attitudes, and practice regarding PV resulted in adequate responses to all three dimensions in only 56.6% of healthcare professionals [23]. These studies indicate that addressing factors that can potentially affect PV is essential for the rapid detection of any type of AEs, including serious and rare AEs. In the current study, dedicated PVCs followed-up participants, thus minimizing under-reporting.

PVCs reported AEs and pregnancies relayed to them by participants to ANVISA via VigiMed; these AEs and pregnancies were unlikely to have been reported otherwise. Nevertheless, the PVCs were unable to contact more than half of the participants when making follow-up calls after these participants had responded "yes". The reasons for the low response to follow-up calls were not investigated and require further study to optimize the use of Seta.

A small study in the Brazilian Amazon investigating the acceptability of phone messages (using short message service [SMS]) as a tool for malaria treatment adherence found that the messages were appreciated [24]. A subsequent larger study found that the phone messages improved treatment adherence and enhanced PV [25]. Limited data network coverage on patients' phones or a reluctance to use internet data by patients with a limited phone plan may have contributed to a low response rate in the current study. In addition, patients without a smartphone did not benefit from the current Seta technology, which can lead to a digital divide in access to healthcare. One option to improve digital inclusion would be to message patients with no or limited access to a smartphone by SMS instead of WhatsApp.

A limitation of this study was the small sample size, although this is the nature of pilot studies. A brief plain language summary is provided for conveying the key information to healthcare professionals and patients (Fig. 2).

Conclusions

This observational pilot study provides insights into how digital reporting tools such as Seta can be used to enhance PV in remote areas and build upon existing signal detection methodologies. AEs and/or pregnancies from 25 out of 149 participants were reported to ANVISA that were unlikely to have been reported otherwise. Therefore, Seta may be useful as an additional tool to complement existing PV and PV tools, especially in geographically challenging areas. Further research on a larger scale could help evaluate the effectiveness and sustainability of the Seta technology in enhancing PV.

Abbreviations

ANVISA	Agência Nacional de Vigilância Sanitária (National Health Surveillance Agency)
AE	Adverse event
DTG	Dolutegravir
HIV	Human immunodeficiency virus
LTFU	Lost to follow-up
PV	Pharmacovigilance
PVC	Pharmacovigilance coordinator
RR	Relative risk
TRuST	Tafenoquine Roll-out STudy

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Trademarks Kozenis is a trademark owned by or licensed to GSK. WhatsApp is a trademark of WhatsApp LLC.

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Author contributions

All authors participated in the design, implementation, analysis, or interpretation of the study, and the development of this manuscript. All authors had full access to the data and gave final approval before submission.

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Availability of data and materials

For requests for access to anonymized subject level data, please contact the corresponding author.

Declarations

Ethics approval and consent to participate

Participant consent was obtained at the clinics through the PVCs or the study website. All information for participants was available in English and Brazilian Portuguese on the Seta study website. The study was approved by the Brazilian Research Ethics Committee (CONEP), reference number CAAE—35245220.8.0000.0005.

Consent for publication

Not applicable.

Competing interests

Dhelio Batista Pereira and Marcus Vinícius Guimarães Lacerda received support from GSK for the conduct of the Seta study. Felix Jackson and Pavandeep Bilkhu are agency workers from medDigital Ltd contracted and paid by GSK to support the setup of the study, develop the Seta application, and write and review the study report. Carolina Duarte and Alex Teckkam were agency workers from medDigital Ltd during the time of the study. Felix Jackson also discloses being a major shareholder in medDigital Ltd. Marcia Rangel, Katie Rolfe, Siôn Jones, Ana Martin, Ioana-Gabriela Fița, Anup Pingle, and Roberto Zajdenverg are employed by and hold financial equities in GSK. Roberto Zajdenverg also received support from GSK to participate in medical conferences as a GSK employee. The authors declare no other financial or non-financial relationships and activities.

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