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BRIEF REPORT

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Impaired creatinine-based estimated glomerular filtration rate in Thai individuals switching to dolutegravir: illustrating the role of cystatin C testing to aid clinical decision making

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Abstract

Introduction Data about impact of switch to dolutegravir (DTG)-based antiretroviral therapy (ART) on estimated glomerular filtration rate (eGFR) in Asians are scarce. RV254/SEARCH010 is a prospective observational cohort in Bangkok, Thailand with ART initiation during acute HIV infection (AHI) where participants switched to DTG-based ART.

Methods Participants started Efavirenz (EFV)-based ART during AHI (n = 214) and switched to DTG-based ART after a median of 97 weeks (IQR 61–145). GFR was estimated by serum creatinine ($eGFR_{cre}$) every 24 weeks before and after switch. Estimated GFR by cystatin C ($eGFR_{cystC}$) was ordered at clinician's discretion for decreased $eGFR_{cre}$ after switch. Random-effect linear regression model was used to assess changes in $eGFR_{cre}$ over 96 weeks from starting ART, and from switching to DTG.

Results At study entry, 20 participants (9.3%) had $eGFR_{cre} < 90$ ml/min/1.73 m^2. During EFV-based ART, an additional 17 (8%) developed $eGFR_{cre} < 90$ ml/min/1.73 m^2, nearly all transient, while mean $eGFR_{cre}$ remained stable and within normal range. At switch to DTG, 21 (9.8%) had $eGFR_{cre} < 90$ ml/min/1.73 m^2 but an additional 116 (54%) developed $eGFR_{cre} < 90$ ml/min/1.73 m^2 during follow-up with $eGFR_{cre}$ decrease being mostly persistent. Mean $eGFR_{cre}$ decreased 20.8% from 117.0 to 92.4 ml/min/1.73 m^2 ($p < 0.001$). Among 20 post-switch participants with $eGFR_{cystC}$ measured within 4 weeks of $eGFR_{cre} < 90$ mL/min/1.73 m^2, 13 (65%) had normal kidney function by $eGFR_{cystC}$.

Conclusions Persistent $eGFR_{cre}$ decrease to < 90 ml/min/1.73 m^2 after switch to DTG was common in this Thai population. $eGFR_{cystC}$ was helpful to identify individuals with clinically significant decrease in kidney function and obviate unnecessary ART modifications.

Trial registration Clinical Trials Registry Number: CliniicalTrials.gov NCT00796146.

Keywords Glomerular filtration rate, HIV infection, Renal insufficiency, Creatinine, Cystatin C, Dolutegravir

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Introduction

Monitoring kidney function is standard of care for people living with HIV (PLWH) due to increased risk of kidney disorders, including drug nephrotoxicity, HIV-associated nephropathy and chronic kidney disease (CKD) [1].

Glomerular filtration rate (GFR) is most commonly used to measure kidney function and to screen for asymptomatic kidney impairment [2], measured directly or estimated by a substance filtered but not actively secreted or reabsorbed by the kidney tubules. Assessing plasma clearance of inulin is the gold standard for direct GFR measurement but is expensive and is not available in most clinical settings. Moreover, inulin or other exogenous markers (e.g. iothalamate, iohexol, DTPA or EDTA), require peripheral administration and 24-h urine collection [2].

Clinically, GFR is usually estimated using serum creatinine level ($eGFR_{cre}$). Creatinine is freely filtered across the glomerulus and neither reabsorbed or metabolized, but undergoes further secretion by an organic cation transporter (OCT2) on the basolateral side of proximal kidney tubule cells [3]. This tubular secretion affects creatinine clearance (CrCl) by contributing approximately 10% to 40% to urinary creatinine. OCT2 is inhibited by certain drugs, causing a decrease in creatinine clearance (CrCl) without affecting true GFR [4]. Other well-known serum creatinine related eGFR confounders are race and muscle mass, with equations estimating GFR evolving over time to best account for such confounders [5].

Cystatin C estimated GFR ($eGFR_{cystC}$) is an alternative measure of kidney function [6, 7] as cystatin C is also freely filtered at the glomerulus and not reabsorbed. It is affected by some other factors than serum creatinine but its metabolism is not affected by OCT2 [8] and it is reported to be more precise and accurate for GFR estimation in Thai PLWH [9].

In 2018, the World Health Organization (WHO) recommended dolutegravir (DTG)-based antiretroviral therapy (ART) as the preferred first-line treatment for PLWH and subsequently, in 2019, as the preferred second-line treatment for those without prior exposure [10]. DTG inhibits OCT2, resulting in elevated serum creatinine and a decreased $eGFR_{cre}$ [11]. In mostly white, healthy volunteers an average decrease in $eGFR_{cre}$ of 10% with DTG 50 mg once daily and 14% with DTG 50 mg twice daily was seen [12]. Virologically controlled PLWH (n = 108, 95% men) in Japan had a median $eGFR_{cre}$ decrease from 74 to 66.5 ml/min/1.73 m^2 ($p < 0.001$) 48 weeks after switching to DTG [13]. Both studies are among multiple reports showing unchanged cystatin C levels after starting DTG and the general utility of cystatin C monitoring for patients receving DTG [14–19]. In the SPRING-1 study, 51 treatment naïve HIV-positive participants (75% white males) receiving DTG 50 mg once daily had mean (SD) decrease in serum creatinine at week 96 of 10.1 (11.07) µmol/L from a baseline of 82.2 µmol/L [20]. In the Spring-2 study 349 treatment naïve HIV-positive participants (majority white males) receiving DTG 50 mg once daily had mean decrease in estimated CrCl at week 96 of 19.6 mL/min [21]. The Spring-2 study did not report on eGFR changes, but only 16/342 participants were reported to have a creatinine increase meeting Division of AIDS (DAIDS) adverse event criteria, with 14 out of 16 being grade 1 (creatinine 1.1–1.3 × upper limit of normal) [22].

We describe incidence and magnitude of decrease in $eGFR_{cre}$ in a Thai cohort for up to 96 weeks after efavirenz (EFV)-based ART initiated during acute HIV infection (AHI), and in the same participants up to 96 weeks after switch to DTG. In a subset of participants on DTG we compare with $eGFR_{cystC}$. This analysis was initiated after more significant decreases in $eGFR_{cre}$ were observed in the study cohort after switch than anticipated from prior studies and the dolutegravir package insert.

Methods

RV254/SEARCH010 cohort participants in Bangkok, Thailand (ClinicalTrial.gov: NCT00796146) started EFV-based ART between March 2010 and November 2016 and switched to DTG-based ART between February 2017 and June 2018 after a median of 97 weeks (IQR 61–145) on EFV. We analyzed $eGFR_{cre}$ levels of this cohort for up to 96 weeks (Median, IQR: 96, 48–96 weeks) pre-switch and up to an additional 96 weeks (Median, IQR: 96, 72–96 weeks) after switch to DTG. The 214 participants included in the analysis are Thai who were stable on EFV-based ART (all but one in combination with tenofovir [TDF] + lamivudine [3TC] OR tenofovir [TDF] + emtricitabine [FTC]), had plasma HIV RNA < 20 copies/mL at time of switch to DTG, and did not use any OCT2 inhibitors (e.g. ritonavir, rilpivirine, cimetidine, or trimethoprim). $eGFR_{cre}$ was calculated at least every 24 weeks before and after switch to DTG. Based on guidelines and terminology of the National Kidney Foundation and DAIDS, kidney function was defined as decreased at eGFR below 90 ml/min/1.73 m^2 and as normal at ≥ 90 ml/min/1.73 m^2 [22, 23]. Decreased eGFR was defined as being persistent if present at at least three time-points over 96 weeks, including the last available measurement. eGFR baseline was considered to be the value upon first starting ART for the period on EFV, and the value upon the day of switch to DTG for the period on DTG. As hepatitis B and C are known predictors of progressive kidney disease in PLWH on ART, sensitivity analysis was done for participants with hepatitis B and/or C to assess whether $eGFR_{cre}$ and $eGFR_{cre}$ changes differed

from the overall cohort [24]. At discretion of treating clinicians, a decline in $eGFR_{cre}$ after switch to DTG was eligible for evaluation with $eGFR_{cystC}$ at any timepoint, using the same blood sample or a repeat blood draw.

The re-expressed Modification of Diet in Renal Disease (MDRD) eGFR formula adjusted for Thai racial factor was used to calculate $eGFR_{cre}$ while $eGFR_{cystC}$ was calculated using the eGFR cystatin C equation. These formulas were selected for reportedly providing values closest to direct kidney function measurement in a Thai cohort of PLWH [9].

Statistical methods

$eGFR_{cre}$ before and changes after switch to DTG were described by mean. Paired t-test was used to compare $eGFR_{cre}$ and $eGFR_{cystC}$. Difference in prevalence of decreased eGFR before and after DTG switch was assessed by McNemar's test. Change in eGFR from baseline was assessed by random-effect linear regression model. A p-value < 0.05 was deemed significant for all calculations. Analyses were performed using StataCorp 2019. Stata Statistical Software: Release 16, StataCorp LLC, College Station, Texas, USA. Figures were generated with GraphPad Prism version 8.2.0 for Windows, GraphPad Software, San Diego, California, USA.

Results

Study population characteristics

Participants' characteristics at ART initiation and at switch to DTG are listed in Table 1. The cohort consists primarily of men who have sex with men (MSM). At time of switch to DTG, participants meeting analysis inclusion criteria were on EFV-based ART for a median (IQR) duration of 97 (61–145) weeks with median $CD4^+$ T-cell count of 637 cells/mm^3. Out of 214 participants, 166 (77.6%) switched from TDF to abacavir (ABC) at time of switch to DTG, while 48 (22.4%) remained on TDF and 45 (21%) had a diagnosis of hepatitis B and/or C.

Table 1 Study population characteristics at ART initiation and at time of switch to DTG

Characteristics	At ART initiation (N = 214)	At switch to DTG (N = 214)
Age (years), median (IQR)	26 (23–32)	28 (24–35)
Sex, n (%)		
Male	211 (98.6)	211 (98.6)
Female	3 (1.4)	3 (1.4)
MSM, n (%)	199 (93.0)	199 (93.0)
CD4 (cells/mm^3), median (IQR)	386 (276–504)	637 (530–762)
HIV RNA (log_{10} copies/mL), median (IQR)	6.01 (5.39–6.84)	N/A*
HIV RNA < 20 copies/mL, n (%)	0 (0)	214 (100.0)
Creatinine (g/dL), mean (SD)	0.91 (0.13)	0.89 (0.13)[a]
$eGFR_{cre}$ (ml/min/1.73 m^2), mean (SD)	115.1 (19.0)	117.0 (19.4)[b]
$eGFR_{cre}$ < 90 ml/min/1.73 m^2, n (%)	20 (9.3)	21 (9.8)
ART regimen, n (%)		
TDF/3TC/EFV	163 (76.2)	–
TDF/FTC/EFV	50 (23.3)	–
AZT/3TC/EFV	1 (0.5)	–
ABC/3TC/DTG	–	166 (77.6)
TDF/3TC/DTG	–	34 (15.9)
TDF/FTC/DTG	–	14 (6.5)
HBsAg positive, n (%)	15 (7.0)	15 (7.0)
Anti HCV positive, n (%)	7 (3.3)	31 (14.5)

Compared to pre-ART values using paired t-test

[a] P = 0.003

[b] P = 0.081

IQR interquartile range, *MSM* men who have sex with men, *N/A* not applicable, *SD* standard deviation, *ART* antiretroviral therapy, *eGFR* estimated glomerular filtration rate, *TDF* tenofovir, *3TC* lamivudine, *EFV* efavirenz, *FTC* emtricitabine, *AZT* zidovudine, *ABC* abacavir, *DTG* dolutegravir, *HBsAg* hepatitis B surface antigen, *HCV* hepatitis C virus

* Study participants were selected for HIV-RNA below level of assay detection at switch to DTG

Mean $eGFR_{cre}$ reduced after switch to DTG

Over the initial 96 weeks on EFV-based ART, mean (SD) $eGFR_{cre}$ did not change significantly from 115.1 (19.0) to 115.4 (18.5) ml/min/1.73 m^2 ($p=0.10$). At switch to DTG, mean (SD) $eGFR_{cre}$ was 117.0 (19.4), also not significantly different from when the cohort first started ART ($p=0.08$). However, at the first available measurement on DTG, 12 weeks after switch, serum creatinine had increased and mean (SD) $eGFR_{cre}$ had decreased significantly by 18.8% (8.0) to 92.8 (15.9) ml/min/1.73 m^2 (both $p<0.001$), with the $eGFR_{cre}$ decrease persisting at all time points thereafter compared to baseline (Fig. 1, $p<0.001$ for all time points after switch). By week 96 on DTG, mean (SD) $eGFR_{cre}$ had decreased by 20.8% (10.9) or 25.6 (14.3) ml/min/1.73 m^2 (both $p<0.001$).

More decreased $eGFR_{cre}$ events after switch to DTG

Upon EFV-based ART initiation 20/214 (9.3%) volunteers had decreased $eGFR_{cre}$, while after a median of 97 (IQR 61–145) weeks on EFV-based ART, at switch to DTG, 21/214 (9.8%) had decreased $eGFR_{cre}$ ($p=0.81$). An additional 17/194 (7.9%) participants developed decreased $eGFR_{cre}$ at any time point while on EFV-based ART vs. 116/193 (54.2%) while on DTG-based ART after the switch ($p<0.001$). New onset decreases in eGFR were transient whilst on EFV-based ART in 87% but were persistent in a majority of 59% after switch to DTG. $eGFR_{cre}$ (mean, SD) did not differ at week 96 after switch to DTG between those who continued TDF and those who switched to ABC in addition to switching to DTG at 90.4 (13.9) ml/min/1.73 m^2 vs. 93.17 (18.0) ml/min/1.73 m^2 ($p=0.433$). No difference was seen between participants

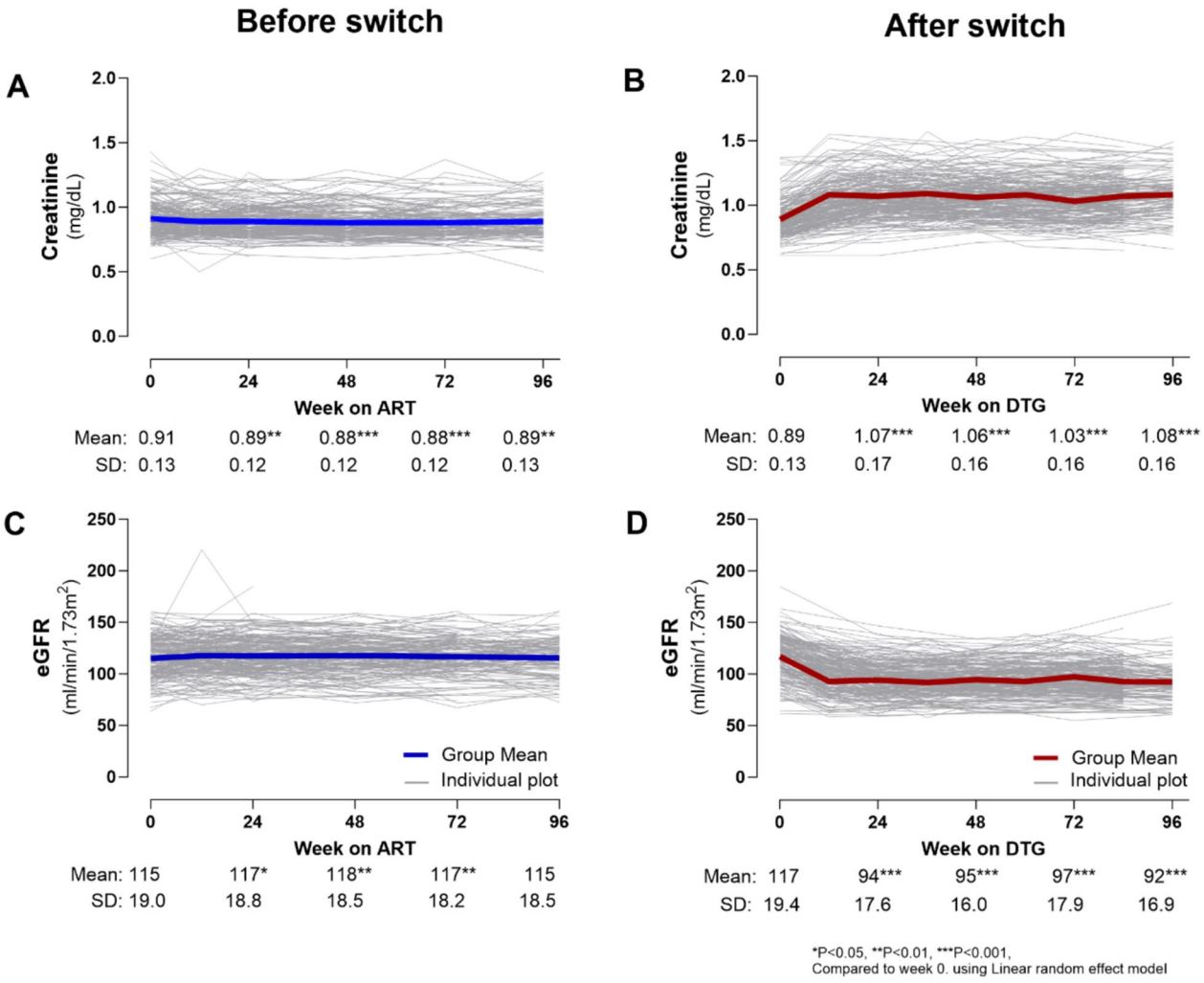

Fig. 1 Creatinine and $eGFR_{cre}$ pre and post switch. Mean creatinine (**A**, **B**) and $eGFR_{cre}$ (**C**, **D**) during 96 weeks on initial ART (**A**, **C**) and during 96 weeks after switch to DTG (**B**, **D**)

with or without hepatitis B and/or C in terms of total creatine, $eGFR_{cre}$, or change in $eGFR_{cre}$.

$eGFR_{cystC}$ is of clinical utility in those with $eGFR_{cre}$ decrease

Twenty eight participants with a decline in $eGFR_{cre}$ after switch to DTG had $eGFR_{cystC}$ measurement within 4 weeks of the decline. The mean (SD) calculated $eGFR_{cystC}$ in these participants was 98.4 (14.6) ml/min/1.73 m^2, significantly higher than mean (SD) $eGFR_{cre}$ at 80.4 (13.0) ml/min/1.73 m^2 ($p < 0.001$) (Fig. 2). Of these 28, 20 had decreased $eGFR_{cre}$ at < 90 ml/min/1.73 m^2, but when cystatin C was used for GFR estimation, 13/20 (65%) had $eGFR_{cystC} \geq 90$ ml/min/1.73 m^2.

Discussion

Dolutegravir administration is associated with an increase in serum creatinine as early as 2 weeks after initiation and a consequent decrease in $eGFR_{cre}$ which persists over time [12, 21]. The Thai participants described here had a mean (SD) $eGFR_{cre}$ decrease of 21.8 (10.2) ml/min/1.73 m^2 or 18.8% (8.0) at 12 weeks after switching to DTG which persisted for the remainder of the 96 weeks observation period.

Koteff et al. reported a phase I study with a decrease in estimated CrCl in healthy, predominantly white volunteers without HIV of 10% on DTG 50 mg once daily and 14% on DTG 50 mg twice daily but with no effect on GFR as measured by iohexol plasma clearance. The SPRING-2 study meanwhile reported a mean decrease in estimated CrCl at week 96 of 19.6 mL/min among 349 participants. Meanwhile, Yukawa et al. reported a median decrease in $eGFR_{cre}$ from 74 to 66.5 ml/min/1.73 m^2 at 48 weeks in an Asian (Japanese) population switching to DTG. Since estimated CrCl tends to be higher than estimated GFR and the Cockcroft-Gault equation estimates CrCl in mL/min while the MDRD equation estimates GFR in mL/min/1.73 m^2, our findings stand out for magnitude and frequency of $eGFR_{cre}$ decrease [25, 26]. Just over 9% of the participants with acute HIV had decreased $eGFR_{cre}$ at study baseline, which is no different from the overall rate in the Thai population [27]. After a median of 97 weeks on EFV-based ART, this proportion was nearly unchanged, still consistent with the overall decreased $eGFR_{cre}$ rate in the Thai population and suggesting no significant ARV drug toxicity.

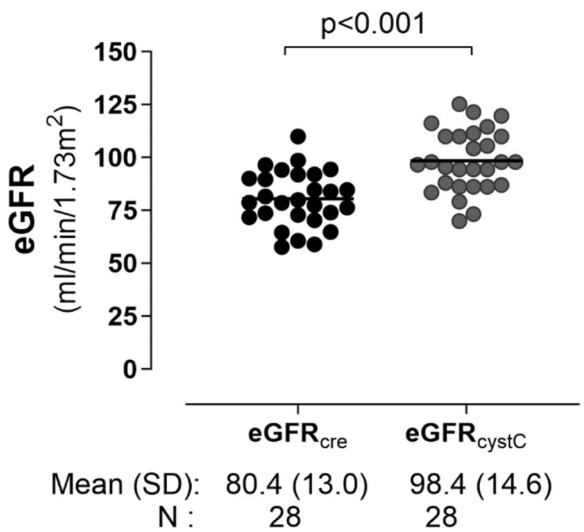

Fig. 2 Creatinine compared to Cystatin C in those with matching samples. Comparison of $eGFR_{cre}$ with $eGFR_{cystC}$ (n = 28)

It is reassuring that among volunteers for whom $eGFR_{cystC}$ was ordered, 65% had no clinically significant decrease in actual kidney function. However, the fact that 35% also had decreased eGFR using cystatin C seems to contrast with prior studies that reported that $eGFR_{cystC}$ did not change after switch to DTG [13–15, 17, 18].

Further study is necessary about the differences observed among these populations and if they can be attributed to race, weight, co-morbidities, or ART history, including protracted tenofovir use in our population.

Our study has several limitations. Cystatin C within 4 weeks of $eGFR_{cre}$ decrease on DTG was only available in 20 of 116 participants with a decrease in $eGFR_{cre}$ below 90 ml/min/1.73 m^2 and selection bias cannot be excluded. Second, our study was performed in predominantly Thai MSM who started ART soon after HIV infection. Further studies are needed to confirm our findings in other Thai and Southeast Asian PLWH.

Conclusions

In our cohort of predominantly young Thai MSM, switch to DTG was associated with more frequent and greater decrease in $eGFR_{cre}$ than expected based on earlier reports [12, 13, 20, 21]. Decreased eGFR after switching to DTG was common when calculated by serum creatinine but not confirmed in 65% of 20 participants for whom cystatin C was available.

As low- and middle-income countries transition to the use of DTG based ART, access to cystatin C measurement or other alternative measurements of GFR for those with marked $eGFR_{cre}$ decrease seems of clinical importance to avoid unnecessary ART modifications.

Abbreviations

3TC	Lamivudine
ABC	Abacavir
AHI	Acute HIV infection
ART	Antiretroviral therapy
AZT	Zidovudine
CKD	Chronic kidney disease
CrCl	Creatinine clearance
DAIDS	Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health

DTG	Dolutegravir
DTPA	Diethylenetriaminepentaacetic acid
EDTA	Ethylenediaminetetraacetic acid
EFV	Efavirenz
FTC	Emtricitabine
GFR	Glomerular filtration rate
eGFR	Estimated glomerular filtration rate
$eGFR_{cre}$	Creatinine based estimated glomerular filtration rate
$eGFR_{cystC}$	Cystatin C based estimated glomerular filtration rate
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
IQR	Interquartile range
MDRD	Modification of diet in renal disease
MSM	Men who have sex with men
OCT2	Organic cation transporter 2
PLWH	People living with HIV
RNA	Ribonucleic acid
SD	Standard deviation
TDF	Tenofovir
WHO	World Health Organization

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Disclaimer
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Author contributions
Conceptualization by CS, DJC, MLR, NP, JA and DH; methodology and analysis by CA, AV and SP; literature search by OG, KP; design and conduct of the clinical trial by CS, EK, DJC, PC, OG, KP, JI, TL, NC, MLR, JA, NP and SV; writing, review and editing by CS, EK, DJC, OG, KP, SP, and DH; all authors have read and approved the final manuscript.

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Data availability
The data that support the findings of this study are available on request from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All participants signed written informed consent and participated in protocols approved by Thai (Chulalongkorn University, Faculty of Medicine, OHRP IRB00001607) and US (Walter Reed Army Institute of Research, OHRP IRB00000794) Institute Review Boards.

Competing interests
The authors declare no competing interests.

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