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RESEARCH ARTICLE

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A retrospective observation of virologically suppressed people living with HIV by comparing switching to BIC/TAF/FTC with initial use BIC/TAF/FTC

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ABSTRACT

Background: The objective of this study was to observe retrospectively the clinical response of virologically suppressed people living with HIV (PLWH) by comparing switching to BIC/TAF/FTC with initial use BIC/TAF/FTC.

Methods: PLWH using BIC/TAF/FTC was divided into 'initial use' group and 'switching to' group. Immune response, metabolic parameters and renal function between the two groups were analysed.

Results: The CD4 cell counts was higher in post- treatment than pre- treatment in the 'switching to' group (416.54 ± 212.11 cells/mm^3 vs. 243.72 ± 156.64 cells/mm^3, $p < .001$); however, significant differences were not observed in the 'initial use' group ($p = .658$). The effect of BIC/TAF/FTC on metabolism was not obvious. Serum creatinine (SCr) was improved in post-treatment than in pre-treatment in 'switching to' group (69.03 ± 18.78 vs. 77.52 ± 20.18, $p < .001$). Platelet count was lower in post-treatment than pre-treatment both in the 'initial use' group (175.81 ± 69.27 vs. 202.90 ± 66.56, $p = .070$) and in the 'switching to' group (177.04 ± 64.48 vs. 212.53 ± 63.43, $p < .001$).

Conclusions: 'Switching to' is superior to 'initial use' BIC/TAF/FTC in immune response among PLWH. The effect of BIC/TAF/FTC on metabolism is not obvious. BIC/TAF/FTC related thrombocytopenia needs to be further explored.

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KEYWORDS
BIC/TAF/FTC; clinical response; initial use; people living with HIV; switching to

1. Introduction

Human immunodeficiency virus (HIV) infection increases the risk of opportunistic infections and cancer [1,2]. Impaired immune function is the most important mechanism caused by HIV [3]. Conducting antiretroviral treatment (ART) as quickly as possible is essential to improve survival by reducing complications and the appearance of new infections of HIV [4]. Over the past years, ART drugs have undergone profound changes that means from muti-drugs to single-tablet regimens which have more favourable adherence [5]. The ideal ART regimens should be excellent efficacy, little toxicity, low drug resistance and convenient administration. Currently, the highly active antiretroviral treatment (HAART) drugs mainly include nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitors (PI), integrase strand transfer inhibitor (INSTI), fusion enzyme inhibitors and nucleocapsid inhibitors [6]. Tenofovir disoproxil fumarate (TDF) + lamivudine (3TC)+efavirenz (EFV) is still commonly used for first-line antiretroviral therapy freely for PLWH in China. Nonetheless, TDF has been associated with nephrotoxicity, such as proximal renal tubulopathy [7]. EFV has been associated with neuropsychiatric (including vivid dreams, dizziness, headache, depression and suicidality) and metabolic side effects that can lead to the discontinuation of therapy [8,9]. Owing to these side effects, some patients have to change the treatment strategy during the course of medication. With the widespread use of INSTI, current international treatment guidelines recommend an INSTI plus 2 NRTIs as preferred initial therapy [6].

Bictegravir (BIC)/tenofovir alafenamide (TAF)/emtricitabine (FTC) is one of the international guideline-recommended treatment for HIV type 1 (HIV-1) in adults, adolescents and children over two years of age and with

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a body weight ≥ 14 kg [10]. Previous data from clinical trials demonstrated that BIC/TAF/FTC has excellent efficacy on virological control, little toxicity, low drug resistance and convenient administration [11]. Real world studies have also demonstrated the safety and efficacy of switching to BIC/TAF/FTC among people with viral suppression and no history of NRTI resistance [12–14]. Positive outcomes about virological suppression, favourable adherence and metabolic profiles were also found after switching to BIC/FTC/TAF in patients with virological failure to PI or NNRTI [15]. However, owing to the influence of various factors, such as patient's economic status and family background, the clinical scene is diverse, which can influence the drug choice of a patient. Not all patients have the financial ability to ART use BIC/TAF/FTC at beginning. Therefore, there are two kinds of ART strategy using BIC/TAF/FTC in clinic: initial use BIC/TAF/FTC and switching to BIC/TAF/FTC. Real-world results found no significant changes in lipid values, blood glucose or liver enzymes, coupled with a significant decrease in viral load either in initial use BIC/FTC/TAF or switching to BIC/FTC/TAF [16]. However, there is still a lack of more real-world evidences retrospectively about clinical effect by comparing the initial therapy with BIC/TAF/FTC with switching to BIC/TAF/FTC in China.

The main objective of this retrospective observation was to compare the clinical immunological responses between initial use BIC/TAF/FTC and switching to BIC/TAF/FTC among virologically suppressed PLWH. Secondary objectives were to assess the impact of switching to BIC/TAF/FTC on metabolic profiles and renal function.

2. Patients and methods

2.1. Study design

PLWH undergoing HAART treatment was screened before 31 June 2022, at the People's Hospital of Yubei District of Chongqing City (Chongqing, China). Patients undergoing HAART treatment with BIC/TAF/FTC were enrolled and were divided into 'initial use' group and 'switching to' group according to the timing of use of BIC/TAF/FTC. All patients in the study achieved effective virological suppression (<1000 copies/ml) and no resistant drugs during ART. Clinical characteristics, immunological response, metabolic profiles and renal function between the two groups were compared.

2.2. Clinical characteristics observation in this study

Clinical characteristics including the white blood cell (WBC) count, platelet count (PLT), haemoglobin (HGB), serum creatinine (SCr), estimated glomerular filtration rate (eGFR), fasting blood glucose (FBG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol (TC), triglyceride (TG), CD4 cell counts and CD4/CD8 ratio were documented at the beginning of BIC/TAF/FTC and evaluated after 48 weeks. All the laboratory tests were performed at the People's Hospital of Yubei District of Chongqing City (Chongqing, China).

2.3. Statistical analyses

Statistical analyses were performed using SPSS 25.0 (IBM, Armonk, NY, USA). Continuous variables were presented as the mean ± standard deviation and then compared using the Student's t-test (when normal distributed) or non-parametric Mann–Whitney U-test (when non - normal distributed). Categorical data were analysed with the chi-squared test and Fisher's exact test. $p < .05$ was considered significant.

3. Results

3.1. First-line antiviral drugs among PLWH

A total of 1903 PLWH with HAART therapy were screened. The number of patients who were given HAART therapy containing INSTI was 230 (12.09%). In addition, 38 patients were excluded because of the therapy regimen not containing BIC/TAF/FTC. Therefore, 192 PLWH using BIC/TAF/FTC were enrolled. Among of them, 42 (21.88%) patients were 'initial use' and 150 (78.12%) patients were 'switching to' BIC/TAF/FTC (Figure 1).

3.2. Immunological responses between 'initial use' group and 'switching to' group among PLWH

The CD4 cell counts and CD4/CD8 ratio were significantly higher in post-treatment than pre-treatment in the 'switching to' group (416.54 ± 212.11 cells/mm^3 vs. 243.72 ± 156.64 cells/mm^3, $p < .001$; 0.72 ± 0.43 vs. 0.31 ± 0.26, $p < .001$, respectively); however, the significant differences were not observed in the 'initial use' group (269.05 ± 163.00 cells/mm^3 vs. 253.48 ± 158.41 cells/mm^3, $p = .658$; 0.47 ± 0.36 vs. 0.43 ± 0.38, $p = .617$, respectively) (Table 1).

3.3. Clinical characteristics of baseline and post-treatment between 'initial use' and 'switching to' group among PLWH

As shown in Table 2, at the baseline and post- treatment stage, the WBC, PLT, HGB, SCr, eGFR, FBG, ALT, AST and

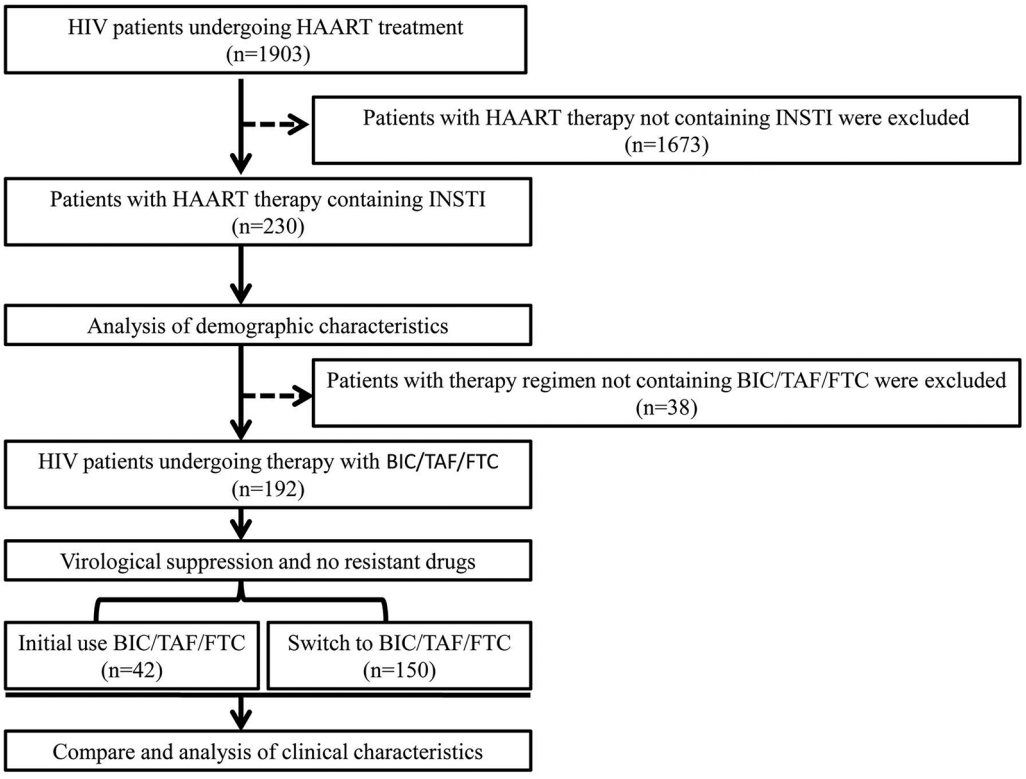

Figure 1. Diagram comparing initial use BIC/TAF/FTC with switching to BIC/TAF/FTC among PLWH.

Table 1. Immunological response between 'initial use' and 'switching to' BIC/TAF/FTC among PLWH.

	Initial use ($N=42$)				Switching to ($N=150$)			
Characteristics	Pre-treatment	Post-treatment	t value	*p* Value	Pre-treatment	Post-treatment	t value	*p* Value
CD4 (cells/mm^3)	253.48 ± 158.41	269.05 ± 163.00	−0.444	.658	243.72 ± 156.64	416.54 ± 212.11	−8.027	<.001
CD4/CD8	0.43 ± 0.38	0.47 ± 0.36	−0.503	.617	0.31 ± 0.26	0.72 ± 0.43	−9.975	<.001

Note: BIC/TAF/FTC: bictegravir/tenofovir alafenamide/emtricitabine; CD4: CD4 cell counts; CD4/CD8: CD4/CD8 ratio; HIV: human immunodeficiency virus; N: number; PLWH: people living with HIV.

Table 2. Clinical characteristics of baseline and post-treatment (48 weeks) between 'initial use' and 'switching to' BIC/TAF/FTC among PLWH.

	Baseline				Post-treatment (48 weeks)			
Characteristics	Initial use ($n=42$)	Switching to ($n=150$)	t value	*p* Value	Initial use ($n=42$)	Switching to ($n=150$)	t value	*p* Value
WBC (*10^9/L)	5.29 ± 1.46	5.25 ± 1.46	0.157	.875	4.82 ± 1.41	5.05 ± 1.62	−0.841	.401
PLT (*10^9/L)	202.90 ± 66.55	212.53 ± 63.43	−0.86	.391	175.81 ± 69.27	177.04 ± 64.48	−0.108	.914
HGB (g/L)	136.82 ± 16.63	139.48 ± 19.69	−0.791	.430	129.75 ± 23.59	136.69 ± 20.01	−1.908	.058
SCr (μmol/L)	79.07 ± 23.76	77.52 ± 20.18	0.424	.672	68.84 ± 19.48	69.03 ± 18.78	−0.055	.956
eGFR (ml/min/1.73m^2)	78.90 ± 24.91	99.06 ± 137.19	−0.946	.345	93.18 ± 29.42	106.46 ± 58.92	−1.41	.160
FBG (mmol/L)	5.85 ± 0.89	5.78 ± 1.44	0.329	.743	5.48 ± 0.78	5.55 ± 1.23	−0.357	.721
ALT (μ/l)	24.32 ± 14.37	38.75 ± 12.92	−1.121	.264	24.75 ± 20.79	30.08 ± 25.02	−1.262	.208
AST (μ/l)	29.90 ± 13.61	34.54 ± 12.33	−0.698	.486	33.37 ± 19.67	31.36 ± 21.54	0.544	.587
TC (mmol/L)	4.25 ± 1.01	4.59 ± 0.94	−2.062	.041	3.97 ± 0.94	4.35 ± 1.83	−1.297	.196
TG (mmol/L)	2.06 ± 0.44	2.42 ± 0.66	−0.297	.766	1.47 ± 0.60	1.33 ± 0.63	1.242	.216

Note: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BIC/TAF/FTC: bictegravir/tenofovir alafenamide/emtricitabine; eGFR: estimated glomerular filtration rate; FBG: fasting blood glucose; HGB: haemoglobin; N: number; PLT: platelet count; SCr: serum creatinine; TC: total cholesterol; TG: triglyceride; WBC: white blood cell count.

TG were not statistically difference ($p>.05$). The level of TC is slightly higher in the 'switching to' group than that of 'initial use' group at the baseline (4.59 ± 0.94 mmol/L vs. 4.25 ± 1.01 mmol/L, $p=.041$); however, the differences were not statistically significant at the post- treatment stage (4.35 ± 1.83 mmol/L vs. 3.97 ± 0.94 mmol/L, $p=.196$).

3.4. Clinical characteristics of pre-treatment and post-treatment between 'initial use' and 'switching to' group among PLWH

The differences of the WBC, HGB, ALT and AST between pre-treatment and post-treatment either in the 'initial use' group or in the 'switching to' group were not significant ($p > .05$). The PLT was lower in post-treatment than pre-treatment both in the 'initial use' group (175.81 ± 69.27 vs. 202.90 ± 66.56, $p = .070$) and in the 'switching to' group (177.04 ± 64.48 vs. 212.53 ± 63.43, $p < .001$). The SCr was slightly lower in post-treatment than pre-treatment both in the 'initial use' group (68.84 ± 19.48 mmol/L vs. 79.07 ± 23.76 mmol/L, $p = .034$) and the 'switching to' group (69.03 ± 18.78 mmol/L vs. 77.52 ± 20.58 mmol/L, $p < .001$). The eGFR was slightly higher in post-treatment than pre-treatment in the 'initial use' group (94.05 ± 29.30 vs. 78.90 ± 23.91, $p = .013$); however, the differences were not observed in the 'switching to' group (106.68 ± 59.06 vs. 99.06 ± 37.19, $p = .534$). The FBG was slightly lower in post-treatment than pre-treatment in the 'initial use' group (5.48 ± 0.78 mmol/L vs. 5.85 ± 0.89 mmol/L, $p = .045$), but the difference was not observed in the 'switching to' group (5.55 ± 1.23 mmol/L vs. 5.78 ± 1.44 mmol/L, $p = .151$). The significant differences of TC and TG in post-treatment and pre-treatment were not observed in the 'initial use' group (3.97 ± 0.94 mmol/L vs. 4.25 ± 1.01 mmol/L, $p = .20$; 1.4 ± 0.60 mmol/L vs. 2.06 ± 0.44 mmol/L, $p = .129$, respectively) or in the 'switching to' group (4.35 ± 1.83 mmol/L vs. 4.59 ± 0.94 mmol/L, $p = .158$; 1.33 ± 0.63 mmol/L vs. 2.42 ± 0.66 mmol/L, $p = .085$, respectively) (Table 3).

4. Discussion

HIV continues to impact millions of people's health care globally and costs billions of dollars annually [17]. ART not only has benefits on the individuals of PLWH, but also prevents the transmission of HIV. Current HIV related international guidelines recommend an INSTI plus NRTIs as preferred initial therapy [6,10]. However, majority of PLWH choose the treatment strategy containing 2 NRTIs plus a NNRTI or a PI because these drugs have been free in China. In this study, we found that 87.91% (1673/1903) patients were on a free regimen without INSTI. Only 12.09% patients received the current internationally recommended regimen containing INSTI. BIC/TAF/FTC is recommended as one of the first-line drug for HIV-1 by international guidelines because of its high resistance barrier, good clinical efficacy, few side effects and convenient administration [6,18–20]. However, among the 192 patients who received internationally recommended BIC/TAF/FTC, only 21.88% (42/192) patients initially received BIC/TAF/FTC therapy and 78.12% (150/192) patients switched to BIC/TAF/FTC only after using the free regimen, owing to severe side effects. BIC/TAF/FTC is less likely to discontinue their regimen than those on any other regimen [21]. Therefore, although the decision-making process regarding ART selection in HIV are complex, popularizing the latest HIV ART knowledge for PLWH patients and medical workers is essential to improve the quality of life of PLWH in China. Among the 192 patients, nearly half of them were late diagnosed HIV infection at admission (defined as CD4 cell count <200/μl at admission [22]). Improving the HIV testing guidelines in China is important to identify individuals with HIV without delays to provide them with timely HIV medical care and treatment.

HIV mainly damages the immune system of the human body; therefore, it is necessary to evaluate the immune reconstitution effect of ART regimens. In the past, many studies focused on the immunological outcomes between the initial use of BIC/TAF/FTC and other INSTIs [18,21,23] and only a few studies exist on whether there is any difference in the immunological response between the initial use of BIC/TAF/FTC and

Table 3. Clinical characteristics of pre- treatment and post- treatment (48 weeks) between 'initial use' and 'switch to' BIC/TAF/FTC among PLWH.

	Initial use ($N = 42$)				Switching to ($N = 150$)			
Characteristics	Pre-treatment	Post-treatment	t value	*p* Value	Pre-treatment	Post-treatment	t value	*p* Value
WBC (*10^9/L)	5.28 ± 1.46	4.82 ± 1.41	1.489	.140	5.25 ± 1.46	5.05 ± 1.62	1.103	.271
PLT (*10^9/L)	202.90 ± 66.55	175.81 ± 69.27	1.828	.070	212.53 ± 63.43	177.04 ± 64.48	4.805	<.001
HGB (g/L)	136.84 ± 16.63	129.75 ± 23.59	1.592	.115	139.48 ± 19.69	136.69 ± 20.01	1.213	.226
SCr (μmol/L)	79.07 ± 23.76	68.84 ± 19.48	2.157	.034	77.52 ± 20.18	69.03 ± 18.78	3.772	<.001
eGFR (ml/min/1.73m^2)	78.90 ± 24.91	94.05 ± 29.30	−2.527	.013	99.06 ± 37.19	106.68 ± 59.06	−0.623	.534
FBG (mmol/L)	5.85 ± 0.89	5.48 ± 0.78	2.039	.045	5.78 ± 1.44	5.55 ± 1.23	1.439	.151
ALT (μ/l)	24.32 ± 14.37	24.75 ± 20.79	−0.111	.912	38.75 ± 12.92	30.08 ± 25.02	1.226	.221
AST (μ/l)	29.90 ± 13.61	33.37 ± 19.67	−0.938	.351	34.54 ± 12.33	31.36 ± 21.54	0.820	.413
TC (mmol/L)	4.25 ± 1.01	3.97 ± 0.94	1.293	.200	4.59 ± 0.94	4.35 ± 1.83	1.415	.158
TG (mmol/L)	2.06 ± 0.44	1.47 ± 0.60	1.525	.129	2.42 ± 0.66	1.33 ± 0.63	1.734	.085

Note: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BIC/TAF/FTC: bictegravir/tenofovir alafenamide/emtricitabine; eGFR: estimated glomerular filtration rate; FBG: fasting blood glucose; HGB: haemoglobin; N: number; PLT: platelet count; SCr: serum creatinine; TC: total cholesterol; TG: triglyceride; WBC: white blood cell count.

switching to BIC/TAF/FTC. As per our results, after 48 weeks of treatment, virological inhibition was achieved both in 'initial use' group and 'switching to' group, which is consistent with previous reports [14]. After 48 weeks of treatment, the CD4+ cell counts and CD4/CD8 ratio in the 'switching to' group were significantly higher than the pre-treatment baseline; although the CD4+ cell counts and CD4/CD8 ratio in the 'initial use' group were also indicated an increased trend, no statistical difference was noted. In addition, CD4/CD8 ratio recovery to ≥1 was not detected between the two groups. This result is inconsistent with the previous reports that mention BIC/TAF/FTC initiation is associated with faster CD4 cell counts recovery [23]. The mechanisms by which switching to BIC/TAF/FTC is superior to initiation use B/F/TAF in immune response among PLWH are unknown.

Metabolic abnormality is a common concern when using BIC/TAF/FTC [24]. In this study, the level of TC was slightly higher in the 'switching to' group than in the 'initial use' group at the baseline; however, after 48 weeks of treatment, the differences were not statistically significant at the post- treatment stage. The level of TG did not change much before and after using BIC/TAF/FTC. The FBG was slightly lower in post-treatment than pre-treatment in the 'initial use' group; however, the difference was not observed in the 'switching to' group. Whether BIC/TAF/FTC has a significant effect on metabolism is controversial [25]. The underlying reason of dyslipidaemia are multifactorial and may be related to sex, genetics, ethnicity, appetite and energy regulation [26]. Minor dyslipidaemia associated with BIC/TAF/FTC should be negligible compared to the clinical efficacy of virological suppression and immune recovery achieved during BIC/TAF/FTC use.

For long-term use of drugs, its safety must be considered. Renal toxicity is the main shortcomings of TDF. TAF, the component used in BIC/TAF/FTC, has lower plasma concentrations and little observed renal or bone toxicity [27,28]. In this study, no statistically significant differences in SCr and eGRF between the two groups at baseline or post-treatment were observed. However, when we analysed the intra-group data again, in the 'initial use' group, the renal function was found to have improved significantly at post-treatment than at pre-treatment, characterized by a decrease in SCr level and accompanied by an increase in eGFR. In the 'switching to' group, the renal function was also improved significantly at post-treatment than that of pre-treatment, characterized by a decrease in SCr level. This suggests that TAF-containing BIC/TAF/FTC is safe for the kidneys, which is consistent with previously reported five-year data on BIC/TAF/FTC [20].

In this study, a rapid increase in CD4 cell counts was accompanied by a decrease in PLT levels in the 'switching to' group. Several therapeutic agents can cause thrombocytopenia by either immune-mediated or non-immune-mediated mechanisms [29]. Whether this phenomenon is due to the toxic effects of the BIC/TAF/FTC or the immune thrombocytopenia has not been reported. The detailed mechanism still needs to be further explored in the following research.

5. Conclusions

Switching to BIC/TAF/FTC among PLWH led to improvements in CD4 cell counts, CD4/CD8 ratio, eGFR and SCr. BIC/TAF/FTC's effect on metabolism is controversial. BIC/TAF/FTC related thrombocytopenia needs to be further explored.

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Ethics approval

The study was approved by the Clinical Research Ethics Committee of the People's Hospital of Yubei District of Chongqing City (Chongqing, China) (Grant no.: 2023GRKHIV1212).

Consent form

Appropriate informed consent was obtained from patients or their legal surrogates before data collection. All authors approved the final version of the manuscript and consented for publication.

Author contributions

Jian Xu contributed to the conception of the thread. Xianghua Dai and Li Huang collected the data. Yuzhi Shi drafted the manuscript. All authors approved the final version of the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The original data in this study can be obtained from the corresponding author upon reasonable request.

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