Randomized trial of

tenofovir disoproxil fumerate dose adjustment VS. switching to tenofovir alafenamide

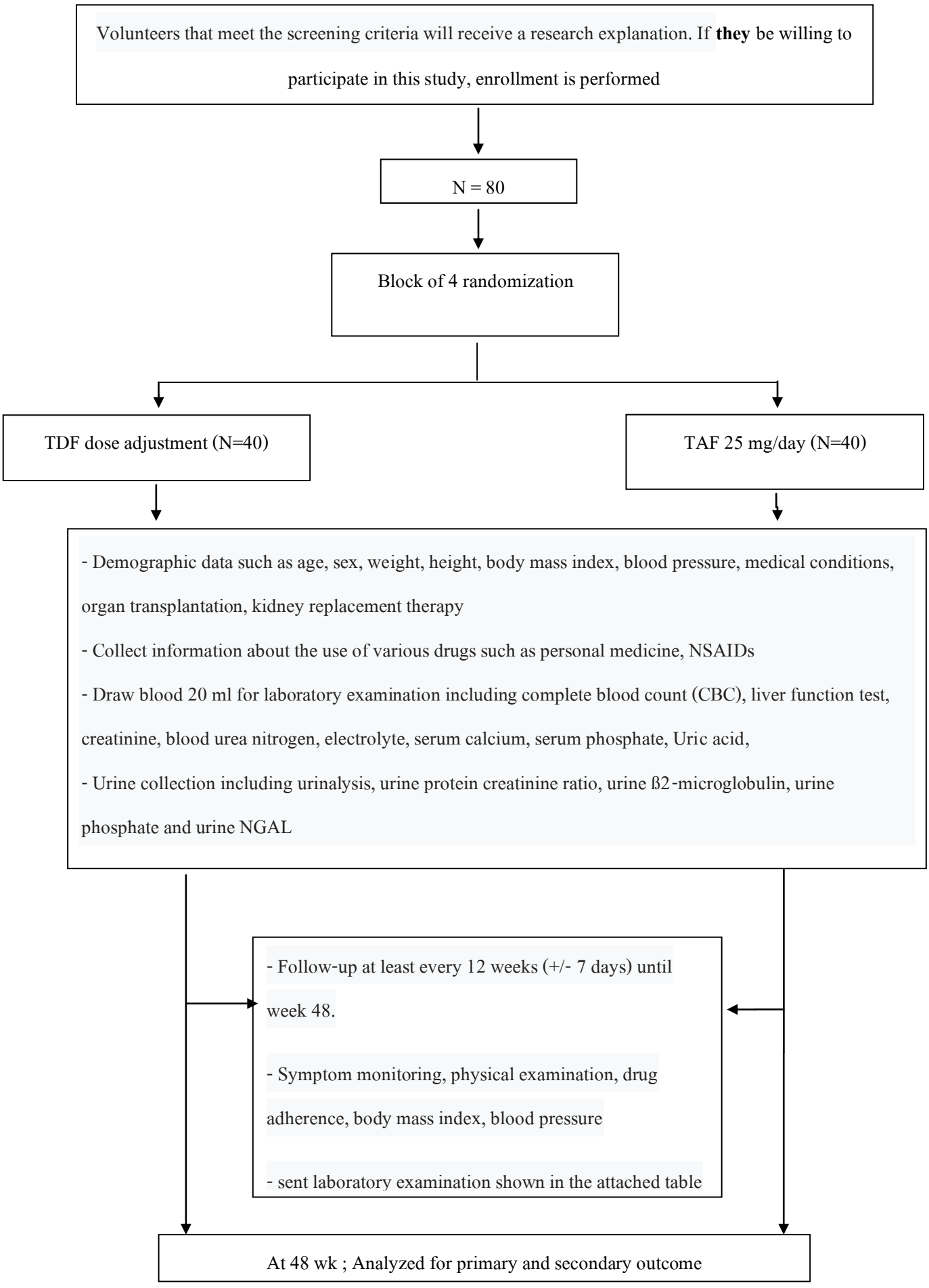
in tenofovir disoproxil fumarate-experienced chronic hepatitis B patients with renal impairment

SIRB Protocol No. : 657/2562(EC3)

COA no. : SI 798/2019

Document date : 25 Nov 2019

Study protocol



	Week 0	Week 12	Week 24	Week 36	Week 48
History taking and physical examination	**X**	**X**	**X**	**X**	**X**
CBC	**X**				**X**
Creatinine, BUN, Uric acid, Calcium, Phosphate, Electrolyte	**X**	**X**	**X**	**X**	**X**
AST/ALT	**X**	**X**	**X**	**X**	**X**
HBV DNA viral load			**X**		**X**
urinalysis, urine protein creatinine ratio, urine phosphate	**X**	**X**	**X**	**X**	**X**
urine ß2-microglobulin	**X**	**X**	**X**		**X**
urine NGAL	**X**	**X**			
ultrasonography of upper abdomen			**X**		**X**

- Some blood tests may be stored before -20 ° C for later tests.
- Some urine tests may be stored before -30 ° C for later tests.

Monitoring and follw-up guidelines in the event that patients receiving TDF dose adjustment or change to TAF and the kidney function deterioration.

- If the GFR from 40 ml/min or more: Make appointment for examination every 12 weeks
- If the GFR is less than 40 ml/min: Make appointment every month

- If the GFR is less than 30 ml/min: Change to Entecavir (1mg) 1 * 1 po pc

If patient will have to check up earlier than 12 weeks, there will be a travel cost of 300 baht per time. However, if the patient comes to the same appointment every 12 weeks, there will be no travel cost.

Inclusion criteria

1. Age between 18 - 75 years old

2. Chronic hepatitis B virus infection

3. Reduced renal function and need to adjust the dose of TDF

4. Have an eGFR of ≥ 15 ml / min.

5. HBV DNA viral load levels ≤ 10 U/mL in the last 3 months before participating in the project

6. No HCC by ultrasonography of the upper abdomen or CT 3-phase of liver or MRI liver in the 3 months before participating in the project.

Exclusion criteria

1. HIV infection or hepatitis C or hepatitis D co-infection
2. Decompensated cirrhosis, including variceal bleeding, ascites, hepatic encephalopathy
3. Active hepatocellular carcinoma or during the 3 years after treatment
4. Solid organ transplantation or Bone marrow transplantation
5. Chronic kidney disease caused by glomerulonephritis, tubulo-interstitial nephritis), Obstructive uropathy or autosomal dominant polycystic kidney, and Kidney disease from other causes
6. Diabetes with HbA1c> 8 or uncontrollable hypertension
7. Active malignancy of cancer in other organs in the last 3 years
8. History of receiving non-steroidal anti-inflammatory drugs (NSAIDs) or other nephrotoxic drugs within the past 1 month (except tenofovir)

(For patients receiving NSAIDS after participating in this study, patients were advised to stop taking NSAIDs but not exclude from the study)

9. Receive immunosuppressive drug

10. Pregnancy

Withdrawal or termination criteria

1. GFR reduction was less than 15 ml / min

2. Receive renal replacement therapy

3. Receive a liver or kidney organ transplant.

4. Request to withdraw from their participation in the study.

5. Develop HCC.

Sample size calculation

From a literature review, It was found that the average value of the eGFR level of the TDF group was -5.34 ± 7.69 (n = 45) (95% CI: -7.65 - -3.02) and the mean value of the eGFR in TAF group was +2.89. ± 4.26 (n = 36) (95% CI: 1.45 - 4.33) But from the Siriraj hospital observations during 2018, the mean The eGFR change value level is +5.92 after TDF dose adjustment. Therefore, from the above data, when determining the significance level = 0.05 (type I error = 5%, 2-sided) and power of the test = 80% (type II error = 20%), 33 samples would be needed in each group

$$n = \frac{\left(Z_{\alpha/2} + Z_{\beta}\right)^2 (\sigma^2)}{(\mu_1 - \mu_2)^2}$$

เมื่อ $n =$ samples would be needed in each group

$\alpha =$ type I error = 0.05 $(Z_{\alpha/2} = 1.96)$

β = type II error = 0.20 $(Z_\beta = 0.84)$

σ = standard deviation

$\mu_1 - \mu_2$ = The difference of mean values between groups

$$n = \frac{(1.96 + 0.84)^2 (4.26^2)}{(5.92 - 2.89)^2} = 33$$

From the calculations, it was found that at least 33 samples were used per group. After add dropout rate 15%, So 40 samples are to be used per group, a total of 80 people in this study.

Statistical analysis

8.8.1 Descriptive statistics

Demographic data such as qualitative variables such as gender, presented in frequency and percentage.

The quantitative variables, such as age, that are continuous data, presented with the mean and standard deviation (SD) if the data has a normal distribution. However, if the data doesn't have a normal distribution, presented with the median and minimum-maximum values.

8.8.2 Inferential statistics

- Comparison of changes in eGFR, serum phosphate, urine protein creatinine ratio, urine phosphate, urine ß2-microglobulin, AST, ALT, HBV DNA between the treatment with TAF and adjusted dose TDF for 48 weeks by using the Repeated measures ANOVA or Friedman's test.

- Comparison of the change in urine NGAL between the treatment with TAF and adjusted dose TDF for 48 weeks by using Independent T test or Mann whitney test

Data recording and analysis using SPSS programme