

### Study of B2 Glycoprotein I antibodies In HIV seropositive patients on hemodialysis

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**Abstract:** There is increasing evidence that infection with HIV may be associated with a hyper-coagulate state. In our study we assessed the frequency of anti- $\beta$ 2 glycoprotein I antibodies and its possible relation to thrombotic complications including vascular access dysfunction in HIV seropositive patients in a sample of Egyptian patients with chronic kidney disease on conservative treatment or regular hemodialysis. This study conducted on forty patients with seropositive HIV antibodies randomly selected from HIV and nephrology departments of Abbassia fever hospital. Ten healthy control subjects were involved. The included patients and controls were divided into 4 groups as follows: **Group 1:** 10 healthy control subjects. **Group 2:** 20 patients with sero-positive HIV antibodies. **Group 3:** 10 HIV patients with chronic kidney disease on conservative treatment. **Group 4:** 10 HIV patients with chronic kidney disease on hemodialysis. All patients and controls were subjected to the following: A detailed history taking and full clinical examination, CBC, ESR, CRP, B2GpI antibodies (IgM and IgG), BUN, serum creatinine, serum Na, Serum K, Serum Po<sub>4</sub>, Serum albumin, total proteins, AST, ALT, coagulation Profile (PT, PTT, INR) and assessment of the fistula flow by Doppler ultrasound. Results of serum B2GPI IgG and IgM in patients groups and control subjects showed that, both B2GPI I gG and IgM showed an increase in serum of patients groups, the statistical analysis revealed a non-significant difference between all the included groups and controls. **Conclusion:** Based on the recorded clinical and biochemical data, the frequency of anti- $\beta$ 2 glycoprotein I antibodies and its possible relation to thrombotic complications including vascular access dysfunction in the included HIV seropositive patients with chronic kidney disease on conservative treatment or regular hemodialysis cannot be efficiently elaborated.

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#### 1. Introduction

Beta 2 glycoprotein I ( $\beta$ 2GPI) implying an important biological function *In vivo*. It binds to negatively charged phospholipids (Roubey, 2000). The positively charged phospholipids binding site of the protein also known as the lysine-binding region, is located in the fifth domain of the molecule.  $\beta$ 2GPI also binds to the surface of endothelial cells (EC) through its fifth domain (Del Papa *et al.*, 1998). The protein is largely synthesized in the liver but  $\beta$ 2GPI mRNA has been isolated from different cell types involved in the pathology of antiphospholipid syndrome (APS) (Chamley *et al.*, 1999).  $\beta$ 2GPI has anticoagulant properties *in vitro* including the inhibition of ADP-induced aggregation of platelets and inhibition of the prothrombinase complex (Roubey *et al.*, 1995). The term antiphospholipid syndrome was coined in the early 1980s to describe a unique form of autoantibody-induced thrombophilia, whose hallmarks are recurrent thrombosis and pregnancy complications (Hughes, 1993). The clinical spectrum of this syndrome has widened, with

important advances in the knowledge of its pathogenesis and clinical management made during the past several years (Cervera *et al.*, 2002; Levine *et al.*, 2002).

Human immunodeficiency virus HIV/Acquired immunodeficiency syndrome (AIDS) prevalence rates are low in Egypt at less 0.1 % in the general population (Abdel-Rasik, 2005). However, United Nations agencies UNAIDS and UNICEF and those working within the Egyptian National AIDS programme (NAP) fear a significant increase in this traditionally conservative society (El-Sayed *et al.*, 2004; Anon, 2007).

There is increasing evidence that infection with HIV may be associated with a hyper coagulate state. The incidence of thrombotic events in Human Immunodeficiency Virus (HIV)-infected patients is rising as suggested in recent retrospective cohort studies (1% - 2%, which is 10 times that expected among people without HIV), but the underlying etiology remains uncertain (Ahonkhi *et al.*, 2008).

**Aim of study:**

This aim of the study is to assess the frequency of anti- $\beta$ 2 glycoprotein I antibodies and its possible relation to thrombotic complications including vascular access dysfunction in HIV seropositive patients in a sample of Egyptian patients with chronic kidney disease on conservative treatment or regular hemodialysis.

## 2. Patients and Methods

This study conducted on forty patients with seropositive HIV antibodies randomly selected from HIV and nephrology departments of Abbassia fever hospital. Ten healthy control subjects were also involved.

### The included patients and control were divided into 4 groups as follows:

**Group 1:** 10 healthy control subjects.

**Group 2:** 20 patients with sero-positive HIV antibodies.

**Group 3:** 10 HIV patients with chronic kidney disease on conservative treatment

**Group 4:** 10 HIV patients with chronic kidney disease on hemodialysis.

### Exclusion Criteria:

1 – Diabetes Mellitus.

2 – Collagen Disorders.

3 – Smoking.

4 – Coagulation abnormalities other than associated with chronic liver disease including drug induced liver disease.

5 – HCV and HBV + Ve patients.

### All patients were subjected:

1 – Full history and clinical examination including vascular access examination (synthetic or native fistula or catheter).

### 2 – Laboratory investigations:

a) B2GPI antibodies (IgM and IgG) titre assays by ELISA.

b) Routine complete blood count (CBC).

c) ESR and quantitative CRP.

d) Routine chemistry including (BUN, serum creatinine, serum Na, serum K, serum  $PO_4$ , serum albumin, total proteins)

e) Liver enzymes (AST, ALT).

f) Routine coagulation profile (PT, PTT and INR).

g) Assessment of fistula flow by Doppler ultrasound.

h) Other investigations whenever needed.

### Specimen Collection:

Under complete aseptic technique, 10 ml of blood was taken from all subjects. Blood was allowed to clot naturally in a test tube. Serum was separated, divided into small aliquots and stored till being tested. Another sample was collected on EDTA for assay of hematological parameters.

### Statistical Analysis:

Data were represented as Mean  $\pm$  Standard error The data were analyzed by One way analysis of variance (ANOVA) using SPSS version 16. Of mean (M  $\pm$  SE). For the statistical test a  $p$  values than 0.01 and 0.05 was taken as significant. The correlation coefficients for serum levels of B2GPI and clinical parameters were calculated using Spearman's test.

## 3. Results

The current study included 40 patients with seropositive HIV antibodies and 10 healthy control subjects were also involved. The included patients and control were divided into 4 groups as follows:

**Group 1:** 10 healthy control subjects.

**Group 2:** 20 patients with sero-positive HIV antibodies.

**Group 3:** 10 HIV patients with chronic kidney disease on conservative treatment.

**Group 4:** 10 HIV patients with chronic kidney disease on hemodialysis.

### - Comparison between patient's groups and control according to age and sex distribution

Data summarized in table 1 showed the age and sex distribution in the control and patients groups. Group 1 involved 10 women, group 2 involved 12 men and 8 women, group 3 included 10 men and group 4 included 8 men and 2 women.

The recorded results about the age distribution revealed that the mean age of the studied groups were 29.50, 31.20, 35.80 and 43.40 for groups 1, 2, 3 and 4, respectively. Groups 4 age showed a significant difference when compared to group 1 and group 2.

Table (1): Comparison between patient's groups and control according to age and sex distribution

	Group 1 (N=10)	Group 2 (N=10)	Group 3 (N=10)	Group 4 (N=10)	P value	Significant
Age (Years)	29.50 $\pm$ 1.73	31.20 $\pm$ 1.17	35.80 $\pm$ 2.89	43.40 $\pm$ 3.48	< 0.001	S
Sex	Women = 10	Men = 12 Women = 8	Men = 10	Men = 8 Women = 2	--	--

### Comparison between serum B2GPI IgG and IgM in patient's groups and control:

Result of serum B2GPI IgG and IgM in patient's groups and control subjects were represented in table 2. Although both B2GPI IgG and IgM

showed an increase in serum of patients groups, the statistical analysis revealed a non – significant difference between all the included groups and control.

**Table (2): Comparison between serum B2GPI IgG and IgM in patient's groups and control**

	Group 1 (N=10)	Group 2 (N=10)	Group 3 (N=10)	Group 4 (N=10)	P value	Significant
B2GPI IgG	0.90 ± 0.14	1.63 ± 0.33	1.65 ± 0.52	1.92 ± 0.45	0.3814	NS
B2GPI IgM	2.44 ± 0.43	3.48 ± 0.52	3.38 ± 0.83	3.38 ± 0.74	0.6633	NS

#### Comparison between serum clinical chemistry parameters in patient's groups and control

Serum BUN showed a significant ( $P < 0.001$ ) increase in group 3 and group 4 patients when compared to the respective control subjects and group 2 patients as demonstrated in table 3. Group 4 patients exhibited significantly ( $P < 0.01$ ) elevated serum BUN levels when compared to group 2 patients.

Similarly, serum creatinine concentration showed a significant ( $P < 0.001$ ) elevation in group 3 and group 4 patients when compared to both group 1 and 2. In addition, serum creatinine of group 4 patients was significant ( $P < 0.01$ ) increased when compared to group 3 patients.

In contrast, serum levels of both sodium and potassium showed a non – significant ( $P > 0.05$ )

between the patients groups and the control subjects. On the other hand, serum phosphorous levels were significantly increased in groups 3 and 4 when compared to group 1 and group 2 as represented in table 3.

Albumin was significantly ( $P < 0.05$ ) decreased in the serum of patients of group 3 and 4 when compared to group 1 subjects (Table 3). On comparison with group 2, serum albumin was significantly decreased in group 3 ( $P < 0.00$ ) and group 4 ( $P < 0.01$ ) patients. More or less similar, serum total proteins were significantly ( $P < 0.01$ ) declined in serum of group 3 and 4 when compared to group 1 subjects.

**Table (3): Comparison between serum clinical chemistry parameters in patient's groups and control**

	Group 1 (N=10)	Group 2 (N=10)	Group 3 (N=10)	Group 4 (N=10)	P value	significant
BUN (mg/dl)	11.3 ± 0.91	13.52 ± 1.12	49.64 ± 8.49	79.79 ± 8.10	<0.0001	S
Creatinine (mg/dl)	0.92 ± 0.06	0.84 ± 0.03	3.08 ± 0.47	8.28 ± 1.09	<0.0001	S
Na (mEq/L)	139.30 ± 0.72	138.30 ± 0.82	125.00 ± 13.55	132.40 ± 2.55	0.2972	NS
K (mEq/L)	4.06 ± 0.14	4.08 ± 0.12	5.36 ± 0.99	4.91 ± 0.33	0.1112	NS
P (mEq/L)	3.41 ± 0.25	3.25 ± 0.16	4.07 ± 0.45	5.51 ± 0.70	0.0004	S
Albumin (g/dl)	4.31 ± 0.23	4.56 ± 0.17	3.32 ± 0.30	3.39 ± 0.16	<0.0001	S
T. protein (g/dl)	8.41 ± 0.29	7.77 ± 0.21	7.04 ± 0.31	6.94 ± 0.19	0.0013	S

#### Comparison between serum CRP in patient's groups and control

Serum CRP levels in group 3 patients exhibited a significant increase when compared to the control ( $P < 0.05$ ) and group 2 ( $P < 0.001$ ) patients as represented in table 4. Group 4 patients exhibited a significant ( $P < 0.001$ ) increase in serum CRP levels compared to group 1 and group 2. In addition, the difference between serum CRP in group 3 and group 4 was significant ( $P < 0.001$ ).

#### Comparison between coagulation parameters in patient's groups and control.

Data concerning the comparison between coagulation factors in control and patients are summarized in table 5. Group 4 patients exhibited a significantly increased PT when compared to group 3 ( $P < 0.01$ ), group 2 ( $P < 0.001$ ) and the respective controls ( $P < 0.01$ ). INR of group 4 patients exhibited the same behavioral pattern while PTT showed a non-significant ( $P > 0.05$ ) change between the patients groups and the control.

**Table (4): Comparison between serum CRP in patient's groups and control**

	Group 1 (N=10)	Group 2 (N=20)	Group 3 (N=10)	Group 4 (N=10)	P value	significant
CRP (mg/L)	4.70 ± 0.23	4.58 ± 0.18	27.28 ± 8.66	64.78 ± 6.68	<0.0001	S

**Table (5): Comparison between coagulation parameters in patient's groups and control.**

	Group 1 (N=10)	Group 2 (N=20)	Group 3 (N=10)	Group 4 (N=10)	P value	significant
PT (Sec)	12.58 ± 0.08	12.44 ± 0.06	12.52 ± 0.06	13.18 ± 0.23	0.0002	S
PTT	29.90 ± 1.28	30.60 ± 0.87	31.50 ± 1.11	32.80 ± 1.17	0.3474	NS
INR	1.08 ± 0.05	1.06 ± 0.04	1.05 ± 0.03	1.74 ± 0.27	0.0241	S

### Comparison between leukocytes and platelets in patient's groups and control.

Concerning the comparing between total leukocytes and its fractions, the data illustrated in table (6) indicated a non – significant ( $P > 0.05$ )

differences between all patients and control. Conversely, platelets showed a significant change in group 4 patients when compared to group 3 ( $P < 0.01$ ), group 2 patients ( $P < 0.001$ ) and the respective control ( $P < 0.001$ ).

**Table (6): Comparison between leukocytes and platelets in patient's groups and control.**

	Group 1 (N=10)	Group 2 (N=20)	Group 3 (N=10)	Group 4 (N=10)	P value	significant
WBCs	7.69 ± 0.39	6.63 ± 0.45	6.65 ± 0.28	6.50 ± 0.30	0.2521	NS
Lymphocytes %	22.42 ± 0.78	21.31 ± 0.91	23.70 ± 1.31	19.39 ± 1.46	0.1040	NS
Monocytes %	1035 ± 1.60	9.57 ± 2.07	8.85 ± 1.73	7.33 ± 0.33	0.0814	NS
Granulocytes %	69.32 ± 1.42	69.07 ± 1.09	67.45 ± 1.31	72.88 ± 1.52	0.0751	NS
Platelets	291.50 ± 14.09	270.50 ± 15.52	263.30 ± 14.94	165.80 ± 13.92	< 0.0001	S

### 4. Discussion

AIDS prevalence rates are low in Egypt at less than 0.1 % in the general population (**Abdel-Rasik, 2005; Country and regional responses to AIDS, 2007**). However, United Nations agencies UNAIDS and UNICEF and those working within the Egyptian National AIDS Programme (NAP) fear a significant increase in this traditionally conservative society (**El-Sayed et al., 2004**) and homosexuals are imprisoned for "habitual debauchery". The changing socioeconomic context with the ongoing economic crisis has in part led to a delay in the age of marriage, which in turn has contributed to an increase in risky behavior (**Abdel-Rasik, 2005**).

In our study, we assessed the frequency of anti-β2 glycoprotein I antibodies and its possible relation to thrombotic complications including vascular access dysfunction in HIV seropositive patients in a sample of Egyptian patients with chronic kidney disease on conservative treatment or regular hemodialysis.

This study conducted on forty patients with seropositive HIV antibodies randomly selected HIV and nephrology department of Abbassia fever hospital. Ten healthy control subjects were also involved.

**- The included patients and control were divided into 4 groups as follows:**

**Group 1:** 10 healthy control subjects.

**Group 2:** 20 patients with sero-positive HIV antibodies.

**Group 3:** 10 HIV patients with chronic kidney disease on conservative treatment.

**Group 4:** 10 HIV patients with chronic kidney disease on hemodialysis.

Results of serum B2GPI IgG and IgM in patient's groups and control subjects were represented in table 4 respectively. Although both B2GPI IgG and IgM showed an increase in serum of patients groups, the statistical analysis revealed a non- significant

difference between all the included groups and control.

Our results are in accordance with the study of Hassoun *et al.* (2004) who reported that HIV infection is known to be associated with an increased prevalence of anti-phospholipid antibodies (aPL). In the same regard, Abuaf (1997) reported on the prevalence of aPL in HIV infection.

Anti-phospholipids syndrome (APS) is one of the few clinical conditions in which patients can present with both venous and arterial thrombosis, with deep vein thrombosis of the lower extremity the most common presentation and stroke the most common arterial manifestation (**Cervera et al., 2002**). Antibodies against phospholipids (PLs) have been commonly found in patients with autoimmune diseases such as systemic lupus erythematosus and primary antiphospholipid syndrome, in which clinical manifestation (mainly thrombotic events) have been directly attributed to antibodies against PLs. In these patients, antibodies against PLs are specific for a neoepitope constituted by the union of β2GPI, lipid binding coagulation inhibitor, to the cellular membrane phospholipids (**McNeil et al., 1990**).

In addition, these antibodies have been observed in some acute viral and bacterial infections as a manifestation of the intense antigenic stimulation of the immune system. These antibodies recognize lipid components of cellular membrane and have no direct role in the coagulation pathway, and their presence probably reflects intense antigenic stimulation of the immune. Because of the lack of a statistical association between these antibodies and development of thrombotic events. The presence of these antibodies is thought to be an epiphenomenon and of no clinical relevance (**Cervera et al., 2004; Sene et al., 2008**).

β2GPI antibodies also have been found on patients with chronic HIV infection, but their association with thrombotic events has not been proven (**Galrao et al., 2007**). However, cases of anti-

phospholipid syndrome in HIV infected patients have been anecdotally reported, prompting clinicians to reconsider the real role of these antibodies, particularly B2GPI antibodies, which are thought to be more specific for anti-phospholipid syndrome. Avascular bone and cutaneous necrosis and deep vein thrombosis and pulmonary emboli were the most common manifestations of anti-phospholipid syndrome (Leder *et al.*, 2001; Ramos – Casals *et al.*, 2004; Shahnaz *et al.*, 2004).

In HIV-infected patients, PL antibodies and  $\beta$ 2GPI antibodies have been strongly linked with level of viral replication (Martinez *et al.*, 2009). The levels of viral load and PL antibodies seemed to run in parallel, with high concentrations of both at hospital admission and simultaneous decline over time. This observation suggests that patients with high levels of viremia, such as those with acute retroviral infection, could be at risk for high titers of PL antibodies and thrombotic events. Testing for antibodies in these patients should be considered as part of routine examination.

Serum BUN and creatinine showed significant increase in-group 3 and group 4 patients when compared to the respective control subjects and group 2 patients. Group 4 patients exhibited significantly elevated serum BUN levels when compared to group 2 patients. On the other hand, serum levels of both sodium and potassium showed a non-significant difference between the patients groups and the control subjects. On the contrary, serum phosphorous levels were significantly increased in group 3 and 4 when compared to group 1 and group 2.

Albumin was significantly decreased in the serum of patients of group 3 and 4 when compared to group 1 subjects. On comparison with group 2, serum albumin was significantly decreased in group 3 and group 4 patients. More or less similar, serum total proteins were significantly declined in serum of groups 3 and 4 when compared to group 1 subjects. These observations may be attributed to the chronic kidney disease combined with HIV in patients of group 3 and 4.

Both AST and ALT showed a non-significant difference between the healthy controls and the patients groups. On the other hand, serum CRP levels in group 3 patients exhibited a significant increase when compared to the controls and group 2 patients. Group 4 patients exhibited a significant increase in serum CRP levels compared to group 1 and group 2. In addition, the difference between serum CRP in group 3 and group 4 was significant. The elevated CRP in group 3 and group 4 are in agreement with (Sentinel *et al.*, 2000) and (Panichi *et al.*, 2000) who stated that serum CRP concentrations have also been found to be significantly elevated in hemodialysis patients and

reflect chronic inflammation, and as an acute-phase reported that, similar to the dialysis population, it was found that serum CRP was elevated in pre-dialysis patients. In addition, a positive correlation between serum CRP levels and several inflammatory factors were found. CRP serum level was also negatively correlated with GFR, the indicator of renal function.

Data concerning the comparison between coagulation factors in control and patients showed that group 4 patients exhibited a significantly increased Pt and INR when compared to group 2, group 3 and the respective control. These findings are in agreement with the study of (Ramaprabha *et al.*, 2014) who reported increased Pt and INR in patients with chronic kidney disease on hemodialysis.

HB% and RBCs in group 3 patients were significantly decreased when compared to group 2 patients and the controls. Hb% of group 4 patients followed the same pattern; where it was decreased significantly compared to group 2, group 3 and the controls. HCT% of patients of both group 3 and 4 showed the same significant changes of HB% and RBCs. While anemia in CKD can result from multiple mechanisms (iron, folate, or vitamin B 12 deficiency; gastrointestinal bleeding; severe hyperparathyroidism; systemic inflammation; and shortened red blood cell survival), decreased erythropoietin synthesis is the most important and specific etiology causing CKD – associated anemia. Erythropoietin is a glycoprotein secreted by the kidney interstitial fibroblasts (Ratcliffe, 1993) and is essential for the growth and differentiation of red blood cells in the bone marrow. In CKD, tubular atrophy generates tubulointerstitial fibrosis, which compromises renal erythropoietin synthetic capacity and results in anemia. The anemia of CKD, increases morbidity and mortality from cardiovascular complications (angina, left ventricular hypertrophy (LVH), and worsening heart failure) (Besarab and Levin, 2000), which may lead to further deterioration of renal function and the establishment of a vicious cycle termed the "cardio renal anemia syndrome".

The presence of LVH is associated with decreased survival of patients on dialysis. In fact, end-stage renal disease patients with LVH have a 30 % lower 5 – year survival rate than individuals lacking LVH (Levin *et al.*, 1996). In addition, anemia is an independent predictor of death in stable coronary artery disease with CKD (Muzzarelli, 2006).

The current study showed that the number of platelets was significantly declined in HIV patients with chronic kidney disease on hemodialysis (Group 4) when compared with group 3, group 2 patients and the respective controls. On the other hand, total leukocyte count and the differentials showed a non – significant difference between all involved patients

and controls. However non-significant, monocytes were decreased in HIV patients when compared to their respective controls and showed more decrease in HIV patients when compared to their respective controls and showed more decrease in group 3 and group 4 patients. Platelets have a primary role in homeostasis as they provide procoagulant PL surface for interaction of coagulation factors. Platelet adherence to injured endothelium is followed by platelet activation, and platelet adherence to injured endothelium is followed by platelet shape change and exposure of PL in the platelet membrane. Platelets circulate in a more activated state in APS have a more prevalent role in arterial clots (Greaves, 1999). Both polyclonal and monoclonal aPL have been shown to activate platelets *in vitro* (Joseph *et al.*, 2001).

Patients with APS often demonstrate mild thrombocytopenia that is not usually associated with bleeding. Platelets sensitized by autoantibodies may be removed from the circulation resulting in lower platelet number. *In vitro*, pretreatment of platelets with low concentrations of another aggregation agonist such as thrombin is required before aPL can induce platelet activation. aPL can only bind to activated platelets and the binding is  $\beta$ 2GPI-dependent (Shi *et al.*, 1993). IgG purified from patients with APS enhance thrombin induced platelet activation and thromboxane B2 (TXB2) formation and complexes of aPL and  $\beta$ 2GPI have been shown to induce increased  $\beta$ 2GPI TXB2 production (Robbins *et al.*, 1998). TXB2 is potent eicosanoid responsible for vasoconstriction and  $\beta$ 2GPI aggregation. It is possible that  $\beta$ 2GPI – anti- $\beta$ 2GPI complexes may prime platelets to be more adherent and susceptible to involvement in clot formation. Parallels have been drawn between heparin- induced thrombocytopenia (HIT) and APS since both are characterized by autoantibody mediated thrombocytopenia and thrombosis in both venous and arterial sites. In both instances the target proteins ( $\beta$ 2GPI or Platelet factor 4) bind to negatively charged molecules resulting in autoantibody formation (Warkentin *et al.*, 2003). Unlike aPL, the antibodies in HIT bind to the Fc<sub>RII</sub> where as antibodies in APS are F(ab)<sub>2</sub> dependant. In HIT PF4/heparin of heparin and PF4 are reached (Warkentin *et al.*, 2003).

Concerning the correlation study between  $\beta$ 2GPI IgG and IgM antibodies and the assayed clinical and biochemical parameters, the results indicated the following:

**In Group 1:** The correlations between B2GPI IgG and IgM antibodies with all the studied parameters were non-significant.

**In Group 2:** B2GPI IgG showed a significant correlation with the age (P=0.002) and ALT (P=0.049)

of group 2 patients. On the other hand, B2GPI IgM showed a significant correlation with BUN (P=0.036) and ALT (P=0.037).

**In Group 3:** B2GPI IgG showed a significant correlation with the age (P=0.025) and ALT (P=0.040) of group 2 patients. On the other hand, B2GPI IgM showed a significant correlation with BUN (P=0.027) and ALT (P=0.029).

**In group 4:** In group 4 patients, there was correlation between B2GPI IgG and monocyte % (P = 0.023).

### Conclusion

Based on the recorded clinical and biochemical data, the frequency of anti- $\beta$ 2 glycoprotein I antibodies and its possible relation to thrombotic complications including vascular access dysfunction in the included HIV seropositive patients with chronic kidney disease on conservative treatment or regular hemodialysis cannot be efficiently elaborated.

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