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RESEARCH ARTICLE

Analysis of Potential Interaction between Antiretrovirals and Comorbid Medications of HIV Patients at a Top Referral Hospital in Indonesia

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Abstract:

Background:

HIV/AIDS usually present with comorbid diseases such as tuberculosis, pneumonia, toxoplasmosis, fungal infections, *etc*., that need multiple medications. Potential interaction between ARV and comorbid drugs is unavoidable.

Objective:

This study aimed to investigate the potential interaction between ARV drugs and medications used to treat comorbid diseases among HIV patients at the Dr. Cipto Mangunkusumo Hospital, Jakarta.

Methods:

This was an observational study using medical record data of 121 HIV/AIDS patients treated at the CM Hospital between January 2016 and July 2017. Potential interaction was classified as "major" if it could lead to increase or decrease of plasma drug levels which potentially result in either drug toxicity or treatment failure, or clinically significant harm to the patient; "moderate" if the interaction is not major, but with the recommendation of close monitoring. National, European, Australian, and Liverpool iChart guidelines were used for the classification of drug interactions.

Results:

Major interactions were noted in 17 (14.05%)patients. Fourteen of them received rifampicin, which potentially decreases plasma level of nevirapine (9 patients), rilpivirine (1 patient), and lopinavir/ritonavir (4 patients). Potential increase of ARV level was found in 3 patients involving interaction between voriconazole-efavirenz (2) and omeprazole-rilpivirine (1). Moderate interaction with the potential decrease of ARV level occurred in 46 patients (38.01%); consisting of a combination of rifampicin with efavirenz (38 pts), rifampicin with zidovudine (6 pts), and phenytoin with efavirenz or nevirapine (2 patients).

Conclusion:

Potential major interaction occurred in 17 (14.05%), which mostly attributed to rifampicin use; while moderate interaction occurred in 46 (38.01%) of patients. Although no serious adverse event was observed in this study, special care should be taken when the drugs with potential major interaction are to be administered

Keywords: Antiretrovirals, Comorbid, Drug interaction, HIV, AIDS, Rifampicin.

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1. INTRODUCTION

Human Immunodeficiency Virus and Acquired Immune Deficiency Syndrome (HIV/AIDS) commonly present with comorbidities, such as tuberculosis, hepatitis, candidiasis, pneumonia, and others that need multiple medications. In this situation, drug-drug interaction that may influence plasma drug levels with the consequences of side effects or treatment

failure, could not be avoided [1, 2]. First-line antiretroviral treatment consists of a combination of Nucleoside Reverse Transcriptase Inhibitor (NRTIs), Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs), and Protease Inhibitor (PIs). Some of the Antiretrovirals (ARV) drugs such as nevirapine, rilpivirine, and lopinavir/ritonavir are mainly metabolized by cytochrome P-450 (CYP450). On the other hand, the treatment of tuberculosis as the most common comorbid needs the use of rifampicin, which is well known as a strong inducer of CYP450. Co-administration of these drugs could lead to a decrease in the ARV plasma level, which may cause HIV treatment failure. Studies on the potential interaction of ARV drugs have been done in several countries. A study in Switzerland reported that 40% of patients showed potential interaction among ARV drugs [3]. A study in Liverpool reported that 27% of 159 patients had the potential ARV interaction, and 15% had a potency to decrease the plasma level of ARV drug [4]. Another study in Kenya in 2011 showed that 33.5% of 996 patients had the potential risk of clinically significant interaction [5]. While a study in Belgium in 2017 reported a 63% potential ARV interaction from 145 patients [6].

USAID data in 2018 noted that 640000 people were living with HIV in Indonesia, and 46000 people have newly been infected with HIV [7]. However, Indonesian data on the profile of comorbidities among HIV/AIDS patients, as well as potential drug-drug interaction between ARV and other medications used for the treatment of comorbidities, are still lacking. This study was aimed at investigating the potential interaction between ARV drugs and concomitant drugs administered to HIV patients at Dr. CiptoMangunkusumo Hospital, Jakarta.

2. MATERIALS AND METHODS

This was a retrospective study conducted on HIV/AIDS inpatient treated at Dr. Cipto Mangunkusumo Hospital medical ward between January 2016 to July 2017. The data were obtained from the medical record of HIV inpatients. The inclusion criteria were patients aged >18 years. Incomplete medical records of those patients were excluded from this analysis.

2.1. Classification of Potential Drug Interaction

References for classification of drug interaction were taken from the Indonesian National Guidelines of Clinical Management of HIV and antiretroviral therapy [8], EAC (*European AIDS clinical society*) guidelines version 9.0 (2017) [9], Australian Society for HIV Medicine (ASHM) guidelines [10], and Liverpool HIV interaction (Liverpool iChart) [11].

Potential of ARV drug interactions were divided into 3 classes: major, moderate, and minor. Major interaction is defined as potentially dangerous interaction which either can lead to drug toxicity, or clinically significant failure of therapy. In the case of major interaction, the software used "*do not co-administer"* or *"contraindication",* or *"avoid",* or *"not recommended"*. Moderate interaction is defined as any plausible interaction that is not included in major interaction but with the warning of potential interaction. In such a case, there will be a recommendation of close monitoring of the patients' condition. Whereas, minor interaction is a condition in which the drug does not have serious interaction or have a mild and not clinically significant interactions. In this study, only major and moderate interactions are reported.

2.2. Data Analysis

Descriptive statistics were used to calculate the percentage of major or moderate interaction between ARV drugs and drugs for treating comorbidities.

3. RESULTS

3.1. Demographic Data

Among the 121 eligible patients for analysis, there were 85 (70.25%) males, and 36 (29.75%) females. The most common (57.02%) age group was between 31-40 years old. The CD4 count on the latest 3-6 months before these data collection was below 50 cells/μL among 68 subjects (56.2%). Ninety-two subjects (76.03%) had been under ARV treatment before inclusion in this study. The most common (64 patients, 52.89%)ARV regiment used was stavudine (d4T) + lamivudine (3TC)+ nevirapine (NVP), followed by tenofovir (TDF) + lamivudine (3TC) + nevirapine (NVP) which accounted in 17 (14.02%) patients. While the combination of zidovudine + lamivudine + efavirenz (or AZT+3TC+EFV), or tenofovir + lamivudine + lopinavir/ritonavir (or TDF+3TC+LPV/r) were used by 12 patients (Table **1**).

Table 1. Characteristics of patients.

Characteristics	N	(%)
Gender		
- Male	85	70.25
- Female	36	29.75
Age (years)		
- < 30	26	21.49
- 31 – 40	69	57.02
- 41-50	20	16.53
- 51-60	4	3.30
- >60	2	1.65
CD4 count (last 3-6 Mo)		
- < 50 - 50-200 - >200	68 37 16	56.20 30.58 13.22
ARV regiment		
d4T+3TC+NVP TDF+3TC+NVP AZT+3TC+EFV TDF+3TC+LPV/r AZT+3TC+NVP d4T+3TC+EFV FTC/TDF+LPV/r Others	64 17 12 12 5 3 2 6	52.89 14.05 9.92 9.92 4.13 2.48 1.65 4.96

Note: d4T = stavudine; 3TC= lamivudine; NVP: nevirapine; TDF = tenofovir; AZT = azido-deoxythymidine (zidovudine); EFV = efavirenz; LPV/r =lopinavir/ritonavir; FTC= emtricitabine; RPV= rilpivirine.

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3.2. Comorbidities

Table **2** shows the distribution of comorbidities in the study subjects. Since one patient may have more than one comorbid, the total number of comorbidities exceeds the total number of patients. The most common comorbidity involved respiratory system (67.77%), with pulmonary tuberculosis being the most frequent (46 patents or 38.02%).

3.3. Drug Interactions

3.3.1. Interaction with Potential Impact on ARV Concentration

The number of drugs used for comorbidity treatment during hospitalization ranged from 2 to 42 drugs (data not shown), averaged 11 drugs/patient. There were 51.24% patients receiving more than 10 drugs. There were 255 drugs used in total, with potential major, moderate and minor interactions.

Table **3** shows that major interactions occurred in 17 (14.05%) patients. Among these interactions, a potential decrease in ARV plasma concentration occurred in 14 patients involving interaction between rifampicin with: nevirapine (9 patients), rilpivirine (1 patient), and -lopinavir/ritonavir (4 patients). While interaction with a potential increase of ARV plasma concentration occurred between rilpivirine-omeprazole (1 patient) and efavirenz-voriconazole (2 patients).

Table 2. Distribution of comorbidities among 121 subjects.

Organ System	Comorbid	n	(%)
Respiratory N=82 (67.77%)	Pulmonary Tuberculosis Pneumonia Pneumocystis Carinii Pleural TB COPD Sinusitis	46 28 3 3 1 1	38.02 23.15 2.48 2.48 0.83 0.83
Gastrointestinal N=60 (49.59%)	Oral Candidiosis Acute Gastroenteritis Dyspepsia Others	27 12 14 7	22.31 9.92 11.57 5.79
Neurology N=56 (46.28%)	Toxoplasma Encephalitis TB Meningitis Epilepsy Polyneuropathy Neurosyphilis Others	26 17 3 1 2 13	21.49 14.05 2.48 0.83 1.65 10.75
Hematology N=37 (30.58%)	Anemia Bicytopenia Pancytopenia Thrombocytopenia Others	20 3 9 2 3	16.53 2.48 7.44 1.65 2.48
Liver N=34 (28.1%)	Hepatitis C Liver Cirrhosis Acute Hepatitis B Chronic Hepatitis B Parenchymal Jaundice Acute Cholangitis	21 2 3 4 2 2	17.35 1.65 2.48 3.31 1.65 1.65
Ophthalmology N=6 (4.96%)	CMV Retinitis Panuveitis Retrobulbar Tumor	2 2 2	1.65 1.65 1.65
Cardiovascular	CAD, HT, Pericardial Effusion	8	6.61
Endocrine N=6 (4.96%)	Type 2 DM SIADH	5 1	4.13 0.83
Lymph Nodes N=8 (6.61%)	Lymphadenopathy Lymphadenitis TB	5 3	4.13 2.48
Urinary Tract N=12 (9.92%)	Chronic Kidney Disease Acute Kidney Injury	5 7	4.13 5.78
Dermato-Venereology N=21 (17.35%)	Venereal Diseases Dermatology	8 13	6.61 10.74
Musculoskeletal	Musculoskeletal	8	6.61
Psychiatrics	Psychiatric Diseases	6	4.96
Other	Sepsis	8	6.61

Table 3. Potential interaction between ARV and concomitant drugs for comorbid treatments.

ARV	Concomitant Drugs	N	(%)	Mode of Interaction
Major Interaction				
NVP	Rifampicin	9	7.44	Decreasing NVP concentration
LPV/r	Rifampicin	4	3.30	Decreasing LPV/r concentration
RPV	Rifampicin	1	0.83	Decreasing RPV concentration
RPV	Omeprazole	1	0.83	Increasing RPV concentration
EFV	Voriconazole	2	1.65	Increasing EFV concentration
Subtotal		**17**	**14.05**	
Moderate Interaction with potential decrease of ARV concentration				
EFV	Rifampicin	38	31.4	Decreasing EFV concentration through induction of CYP3A4.
EFV	Phenytoin	1	0.83	Phenytoin decreases EFV concentration due to induction of CYP3A4.
NVP	Phenytoin	1	0.83	Decreasing NVP concentration
AZT	Rifampicin	6	4.96	Decreasing AUC of AZT
	Subtotal	**46**	**38.01**	
Moderate Interaction with potential increase of ARV concentration				
LPV/r	Fluconazole	2	0.78	Increasing LPV/r concentration due to inhibition of CYP3A4
NVP	Fluconazole	7	2.75	Increasing NVP concentration and risk of hepatotoxicity.
RPV	Fluconazole	1	0.39	Increasing RPV concentration through inhibition of CYP3A4 by fluconazole. Increasing fluconazole hepatotoxicity.
TDF	Streptomycin	24	9.41	Streptomycin increases TDF concentration, but TDF increases streptomycin nephrotoxicity and ototoxicity
TDF	Amikacin	5	1.96	Amikacin increases TDF concentration, but TDF increases amikacin nephrotoxicity.
TDF	Valgancyclovir	4	1.57	Increasing TDF concentration and increasing nephrotoxicity and ototoxicity
TDF	Amphotericin B	4	1.57	Increasing TDF concentration and amphotericin nephrotoxicity
TDF	Acyclovir	3	1.18	Competition during renal tubular secretion and increasing TDF toxicity
TDF	Gancylovir	3	1.18	Increasing TDF concentration and nephrotoxicity
TDF	Gentamycin	2	0.78	Gentamycin increases TDF concentration, but TDF increases gentamycin nephrotoxicity.
TDF	Cisplatin	1	0.39	Increasing TDF concentration through inhibition of elimination. Increasing nephrotoxicity and ototoxicity
AZT	Cotrimoxazole	14	5.49	Increasing AZT concentration due to renal clearance inhibition.
AZT	Fluconazole	4	1.57	Increasing AZT concentration
AZT	Ganciclovir	1	0.39	Increasing AZT concentration
AZT	Valganciclovir	1	0.39	Increasing AZT concentration
AZT	Valproic acid	1	0.39	Increasing AZT concentration
Subtotal		**77**	**63.64**	

Note: NVP: nevirapine; LPV/r: lopinavir/ritonavir; RPV: rilpivirine; EFV: efavirenz; AZT: Azidotymidine (zidovudine); TDF: tenofovir.

Table 4. Interaction with potential impact on comorbid drugs concentration.

ARV	Comorbid Drugs	N	%	Mode of Interaction
Major Interactions				
RPV	Domperidon	2	0.78	Increasing domperidone concentration, potential QT prolongation
RPV	Clopidogrel	2	0.78	Decreasing active clopidogrel concentration
Moderate interactions				
EFV	Diclofenac	3	1.18	Increasing concentration and effect of diclofenacdue to inhibition of CYP2C9.
EFV	Clobazam	2	0.78	Increasing clobazam concentration due to inhibition of CYP2C19.
EFV	Diazepam	2	0.78	Increasing diazepam concentration due to inhibition of CYP3A4.
EFV	Fentanyl	2	0.78	Decreasing fentanyl concentration du to stimulation of CYP3A4.
EFV	Docetaxel	1	0.39	Decreasing docetaxel concentration du to EFV effect of CYP3A4.
EFV	Ibuprofen	1	0.39	Increasing ibuprofen concentration
EFV	Morphine	1	0.39	Increasing morphine concentration by inhibition of UGT2B7.
EFV	Quetiapin	1	0.39	Decreasing quetiapine concentration
EFV	Risperidon	1	0.39	Decreasing risperidone concentration
LPV/r	Ondansetron	9	3.53	Increasing ondansetron concentration with increasing risk of QT prolongation.
LPV/r	Azitromycin	2	0.78	Inducing QT interval prolongation

(Table 4) cont.....

ARV	Comorbid Drugs	N	%	Mode of Interaction
LPV/r	Alprazolam	1	0.39	Increasing alprazolam concentration and effect
LPV/r	Haloperidol	1	0.39	Increasing haloperidol concentration with increasing risk of QT prolongation.
NVP	Fentanyl	2	0.78	Decreasing fentanyl concentration through induction of CYP3A4 by NVP.
NVP	Amloidipin	2	0.78	Decreasing amlodipine concentration and effect
NVP	Risperidon	1	0.39	Decreasing risperidone concentration
d4T	Isoniazid	2	0.78	Increasing neuropathy
TDF	Ibuprofen	2	0.78	Increasing risk of nephrotoxicity
Subtotal		**61**	**50.41**	

Note: NVP: Nevirapine; LPV/r: Lopinavir/ritonavir; RPV: Rilpivirine; EFV: Efavirenz; AZT: Azidotymidine (zidovudine); TDF: Tenofovir.

Moderate interactions that potentially decrease ARV concentration occurred between rifampicin-efavirenz in 38 patients (14.9%), and rifampicin-zidovudine in 6 patients (4.96%)and phenytoin with nevirapine or efavirenz (1 patient each).

3.3.2. Interaction with Potential Impact on Comorbid Drug Concentration

Table **4**. shows interactions with potential impact on comorbid-drugs concentration. Major interaction was detected in 4 patients involving domperidone-rilpivirine(2 patients) with the potential to increase domperidone plasma concentration with the risk of QT prolongation; and between clopidogrel-rilpivirine(2 patients) which potentially inhibit the conversion of clopidogrel into its active form due to inhibition of CYP enzyme by rilpivirine.

4. DISCUSSION

In the present study, the pattern of comorbidity, medication used, and the potential of interactions of HIV and comorbid drugs are reported in HIV patients treated at Cipto Mangunkusumo hospital between January 2016 and July 2017. From 121 patients, about 70.25% were male and most of the patients were in sexually active age (18-41 years). These findings are in accordance with the study of Jiyo *et al*. (2013), who reported that most of the patients were male (61.57%) and the age ranged between 20-40 years [12]. The percentage of the patient with a CD4 level below 50 cells/μL in the last 3-6 months was 56.2%. About 92 Patients (76.3%) have been under ARV therapy. The most common ARV regimen was stavudine + lamivudine + nevirapine, and the second most common was tenofovir + lamivudine + nevirapine.

Comorbidity pattern showed that the number of comorbid ranged from 1 to 8 diseases (median 2.9) with pulmonary tuberculosis being the most common (46 patients or 38.01%), followed by oral candidiasis (27 patients, 22.31%), and toxoplasma encephalitis (26 patients, 21.49%). The study of Jiyo *et al*. also reported the same trend of comorbidities [12]. While another study in Surabaya, Indonesia, showed that the most common comorbidities were diarrhea, lung tuberculosis, and oral candidosis [13].

4.1. Major Drug Interaction

From 121 patients enrolled in this study, potential major interactions were found in 21 patients (17.35%). In 14 of them, a potential decrease of ARV level can be expected, which was related to the interaction between rifampicin with nevirapine (9 patients), Rifampicin With Rilpivirine (RPV) in 1 patient, and rifampicin with lopinavir/ritonavir (4 patients). Rifampicin is well known as a strong inducer of almost all isoenzymes of CYPs. Thus, co-administration of rifampicin will lead to a decreased concentration of other drugs that are metabolized by CYPs, with the potential consequence of therapeutic failure. Special precautions should be made, regarding that both rifampicin and ARV should be taken by patients for long-term treatment. Nevirapine and rilpivirine (the non-nucleoside reversetranscriptase inhibitor), as well as lopinavir (a protease inhibitor) undergo metabolism by CYP3A4 and CYP2B6, while rifampicin is well known as a strong inducer of those enzymes [14], and co-administration between these drugs is classified as a major interaction. In the present study, we did not measure plasma level of nevirapine. However, in another study, Nafrialdi *et al*. [15] showed a significant decrease in nevirapine level during concomitant therapy with rifampicin, even though this level was still in the therapeutic range. The study by Cohen *et al*. [16] in Africa also reported a significant decrease in nevirapine levels in most patients who received concomitant treatment with rifampicin. Efavirenz is recommended as an alternative for nevirapine, due to its moderate dependence on CYP3A4. Limited availability of efavirenz is a major reason why some patients continue to receive nevirapine concomitantly with rifampicin. This justification is supported by the report of Manosuthi *et al*. [17], which states that the use of nevirapine can be considered rational in patients receiving rifampicin in limited resource countries, such as Thailand and Indonesia.

In the case of major interaction between LPV/r and rifampicin as identified in 4 patients, dose adjustment has been performed according to the guideline of HIV treatment 2011: the dose LPV/r was increased to 2x400 mg in 3 patients, and to 2x800 mg in one patient [8]. Meanwhile, in patients who previously received RPV, streptomycin was introduced as a substitution for rifampicin on the 2nd day of treatment.

Interaction between lopinavir and domperidone in two patients was considered major, due to the potential increase of domperidone concentration, which may lead to QT prolongation, with the theoretical consequence of developing arrhythmia. While the interaction between lopinavir with clopidogrel (2 patients) was also considered major since lopinavir acts as an inhibitor of CYP3A4 that could inhibit the activation of clopidogrel with the potential consequence of decreasing clopidogrel's effect. However, no such side effects were observed in this study.

Aside from the interaction that resulted in a decrease in

ARV concentration, interaction that potentially increases the ARV level was observed between voriconazole with efavirenz (2 patients) and omeprazole with rilpivirine (1 patient). Voriconazole and omeprazole are both inhibitors of CYP3A4 that may increase the plasma level of efavirenz and rilpivirine. In this study, since voriconazole and omeprazole were administered for a relatively short period, clinical consequences of the increased level of those two ARVs were not clinically significant.

4.2. Moderate Drug Interaction

Moderate interaction between rifampicin occurred with efavirenz (38 patients) and zidovudine (6 patients). Efavirenz is a NNRTI and zidovudine is a NRTI both of which are metabolized by CYP2B6 and 3A4. Interaction with rifampicin may result in the acceleration of the metabolism of both these drugs that may lead to a decrease in their plasma levels. A study by Yenny *et al*. [18] in healthy subjects showed a decrease in efavirenz bioavailability associated with co-administration with rifampicin. Another study by Ramachandran reported an increase in efavirenz clearance in HIV/TB patients receiving anti-tuberculosis drugs at the same time [19]. However, the rate of efavirenz metabolism may vary among individuals due to the genetic polymorphism of the CYP2B6 enzyme [14]. This finding was supported by the study of Abiy *et al*., in Ethiopia 2015 [20], which also found that the influence of rifampicin on the efavirenz plasma level is influenced by the CYP2B6 genotype. In clinical settings, the interaction between rifampicin and efavirenz is considered non-significant, and efavirenz is usually used as a substitute for nevirapine in patients receiving rifampicin.

Twenty-four patients (19.83%) received tenofovir and streptomycin due to tuberculosis. This combination potentially increases the tenofovir level since streptomycin may inhibit the elimination of tenofovir. This interaction is classified as moderate and has no serious clinical consequences. A high incidence of moderate potential interaction in this study is likely caused by the high number of drugs needed to treat comorbidities, especially in patients with CD4 levels below 50 cells/μL. The study by So-Ngern *et al*. [21] found the existence of a correlation between low CD4level and potential drug interaction, while the study of Kigen reported no correlation between CD4 levels and potential drug interaction [5].

4.3. Clinical Consequences

Among the 9 patients that received rifampicin and nevirapine, 5 of them just started the ARV during the collection of the data. Thus, we were unable to evaluate the clinical consequence of this co-treatment. As previously stated, co-treatment of nevirapine and rifampicin is acceptable, especially in limited resource countries [17]. Thus, this combination was continued in these 9 patients. Four patients had been previously receiving ARV, and 3 of them had a CD4 count of less than 50 cell/μL. Nevirapine was substituted with efavirenz in two of them, while in another patient, this change was not done since the patient suffered from depression, and administration of efavirenz could worsen these symptoms [22].

Overall, we consider that the treating physicians in this study have done good anticipation of potential interaction between ARV drugs and drugs for treating comorbid.

4.4. Limitation of the Study

The main limitation of the study could be attributed to the observational-cross sectional nature of this study. Thus, we were unable to follow the consequences of drug-drug interaction, either on the plasma drug level, or on the treatment outcome. However, in almost all patients, good anticipation has been performed by the treating physicians, and no serious adverse events were found. Another difficulty was related to the references used to judge the potential interaction of drugs, which do not completely match each other.

CONCLUSION

Potential major interaction occurred in 17 (14.05%) patients and moderate interaction occurred in 46 (38.01%) patients, which was mostly attributed to the use of rifampicinin in combination with CYP-substrate drugs. While the potential increase of ARV concentration occurred in patients receiving aminoglycosides, azole antifungi and antiherpetic antiviruses. Although no serious adverse event was observed in this study, special care should always be taken when the drugs with major interaction are to be administered.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The protocol of the study had been approved by Ethic Committee of University of Indonesia with Approval No. 0496/UN2.F1/Etik/2018.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this study are available within the article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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