Prevalence of HIV infection in infatnts exposed to HIV and receieved single dose nevirapine or zidovudine with single dose nevirapine at Yekatit 12 Hospital, addis Ababa

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Abstract

Background: *Antiretroviral treatment decreases the rate of HIV transmission from mother to child significantly. Use of SD NVP has been in use since 2006 up to 2008 when the National recommendation of combination treatment with SD NVP + AZT for a week /month has started. But the effect of these interventions hadn't been assessed in our setup.*

Objectives: *To determine the prevalence of HIV Infection in infants who received either SD NVP or SD NVP with AZT & to assess the morbidity & mortality of patients infected with HIV.*

Methods: *A medical record review of all patients seen at Yekatit 12 hospital and received either SD NVP or SD NVP with AZT has been reviewed.*

Results: *A total of 144 exposed infants who had received either SD NVP or SD NVP with AZT has been retrieved. The sex distribution was comparable and the mean age for DNA PCR & Antibody test at diagnosis was 3.5months & 12 months respectively. The prevalence of HIV Infection in those who took either form of prophylaxis was found to be 12.5% while the rate of HIV Infection in patients who took SD prophylaxis is 15.1% as compared to 7.8% in those who took SD NVP with AZT. From these HIV Infected patients, 88.8% had one or more opportunistic infections in the first 2 years and 16.7% were dead before the age of 2 years.*

Conclusion and recommendation: *Use of combination treatment, AZT with SD NVP, is more effective than SD NVP regimen alone in preventing mother to child transmission but a large scale study is needed to see the effect at large.*

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Introduction

As of July 2006, 38.6 million people were living with HIV/AIDS and more than 27 million had died since the beginning of the epidemic [1]. Of the 38.6 million, 25 million were living in sub-Saharan Africa alone; it is estimated that 15 million children have been orphaned by the premature death of both parents due to AIDS, placing enormous responsibilities on communities, and 2.0 million children are living with HIV/AIDS [1].

Globally in each day, fifteen hundred children become infected as a result of mother-to-infant transmission, despite data that antiretroviral drugs given at the time of delivery and to the infant after birth can largely prevent this [2]. Of the 600,000 infants and children infected with HIV in year 2005, 70% were born in sub-Saharan Africa, 25% in South East Asia, and the remainder in Latin America and the Caribbean [3]. Currently less than 10% of HIV-Infected pregnant women in Sub-Saharan Africa receive any form of Prevention of Mother to Child Transmission (PMTCT) [4].

In Ethiopia, the exact prevalence of HIV in children is not known; however, there are currently 134,586 children under 14 years living with HIV/AIDS and 30,338 new infections in 2005[5].

The major (>90%) mode of acquisition of HIV in children worldwide is through mother-to-child transmission. Without interventions, there is a 20-45% chance that a baby born to an HIV-infected mother will become infected [6].

Antiretroviral drugs (ARV) reduce viral replication and can reduce mother-to-child transmission of HIV either by lowering plasma viral load in pregnant women and/or through post-exposure prophylaxis in their newborns. Transmission has been reduced to less than 2% percent in resource-rich countries with implementation of recommendations for universal prenatal HIV counseling and testing, antiretroviral prophylaxis, elective cesarean delivery and avoidance of breast feeding [7]; but Highly Active Anti-Retroviral Treatment (HAART) is not yet widely available in low and middle income countries & thus various simpler and less costly antiretroviral regimens have been offered to pregnant women &/or to their newborn babies.

Different studies have been done since 1991 to study the effect of ARVs in preventing mother to child transmission. In 2003, the HIVNET 012 TRAIL in Uganda evaluated an intrapartum /newborn regimen of nevirapine (200 mg PO as a single dose) to women at the onset of labor and 2 mg/kg given orally once to the infant at age 48 to 72 hours of age, compared to an ultra-short course of ZDV, given orally intrapartum (600 mg ZDV, then 300 mg ZDV every 3 hours) and for one week to the infant (4 mg/kg twice daily) [10]. The result was a 47% relative reduction in the risk of transmission with nevirapine [10]. Nearly all babies (99%) were breastfed (with median duration of breastfeeding of nine months). Despite breastfeeding, the single-dose nevirapine regimen demonstrated significant persistent efficacy, 41% at age 18 months compared to the ultra-short ZDV regimen (infection rate 15.7 versus 25.8 percent, respectively) [11].

Single dose Neverapine has also been found to significantly reduce breast milk virus for approximately two to three weeks as compared to short course ZDV [13]. In another study, it was found to be equally effective regardless of infant feeding mode suggesting that single-dose nevirapine may uniquely protect against early breast milk HIV transmission occurring during the first few weeks of life, which is likely the highest risk time for breast milk HIV transmission [14].

In another trial done in Malawi (NVAZ Trial) that compares the effect of single dose NVP with that of combination treatment with NVP + AZT in mothers who took no antiretroviral prophylaxis prior to delivery and continued exclusive breastfeeding showed that the rate of infection was 15.3% in SD NVP + AZT arm and 20.9% in SD NVP only arm at 6-8 weeks.

In the following year, a different study was conducted in Malawi, where by the mothers took intrapartum single dose NVP, infants took either single dose Neverapine or NVP + AZT & exclusively breast fed, the rate of mother to child transmission at 6-8weeks in patients not infected at birth was found to be 6.5% in the AZT + NVP arm and 16.9% in the NVP arm [16].This showed a marked improvement in the rate of transmission & was suggested as another effective method to be used as Prevention Of Mother To Child Transmission in resource limited settings.

Generally it has been found that single dose NVP only or single dose NVP with AZT is less expensive and thus is able to be implemented in most developing countries including ours, with proven effectiveness. Use of Sd NVP has been implemented since 2006 and Sd NVP + AZT since 2008 but there hadn't been any research done in our setup to see whether the effect was the same or not & the factors associated with it. The Data collected can be used as base line information by other pediatricians, public health professionals, and Ministry of Health and policy makers. This research is therefore selected to give an overview in our setup & to be a stepping stone for further advanced studies.

Methods and Materials

A descriptive cross sectional study design of all HIV Exposed infants who took SD NVP only or Sd NVP with AZT prophylaxis and whose final result is known were included in the study. The study was conducted at Yekatit 12 Hospital, Addis Ababa from Oct. 2006 – Oct. 2008.

Patients with incomplete medical records and exposed infants who took no prophylaxis were excluded from the study.

A complete list of cases seen from October 2006 till October 2008 was retrieved from Registry log books & the list was used to retrieve the cards.

Data was collected with a help of a prepared questionnaire from the patients cards, PMTCT log books, interviews & phone calls done by the Principal Investigator.

Questionnaire, record, and a check file was developed using SPSS version 17.0. Data was then entered twice & analyzed with SPSS version 17.0.

HIV DNA PCR was performed for all exposed infants less than 18months & a repeat antibody test was done at the age of 1year. If both tests are negative, the child is declared not infected & will be discharged from follow up provided that the patient has stopped breast feeding for greater than 6weeks before the last test.

For patients on replacement feeding since birth, if both tests are negative (i.e. negative antibody test even before the age of 1year), then patient is declared Not Infected.

If DNA PCR is Negative & HIV antibody test at 1year of age is positive, a repeat antibody test will be performed at 18 months of age. If the repeat antibody test is positive then the child is diagnosed as

HIV Infected. If negative, then the child is not infected & will be discharged from follow up clinic. If DNA PCR is positive, the child is HIV Infected & will continue follow up in the ART clinic until 13years of age.

Ethical clearance for the study was obtained from the Department of Pediatrics & Child Health Department of Addis Ababa University

Limitations of the study

DNA PCR at birth is not done in all of the subjects and this might affect the outcome variable since in utero infections cannot be safely excluded. Maternal clinical stage, CD4 Count & viral load during pregnancy couldn't be retrieved that could also affect outcome and small sample size

Results

During the study period from October 2006 to October 2008, there were a total of 144 exposed infants who had taken SD NVP or SD NVP + AZT and on follow up. Of the total 144 infants, 77 (53.5%) were males and 67 (46.5%) were females. Eighteen (12.5%) were found to be positive with final HIV result, whereby 12(66.7%) were males and 6 were females (33.3%). The mean age for DNA PCR test was 3.5months, and the mean age for final antibody test was 12.24 months. All infants whose status was positive with DNA PCR were also positive at the final antibody test.

In the anthropometric measurement of weight for age, the majority, 127 (88.2%) were within normal range whereas 14 (9.7%) were under weight and 3 (2.1%) were marasmic. From these 3 marasmic infants, 2 were found to be HIV positive while 3 (21.4%) cases of HIV positive results were detected from the 14 underweight cases. Table 2 shows the weight- for- age as compared to final HIV result.

When we see the educational status of the mothers, 24(16.7%) were illiterate, 46(31.9%) were less than grade 8, 38(26.4%) were between grade 8 – 12 and 26(18.1%) completed grade 12 and the rest 10(6.9%) graduated from higher institutions. Seven (38.9%) HIV positive infants are born from mothers who are < grade 8 and 3(16.7%) are born from illiterate mothers. Table 3 shows maternal educational status in relation to final HIV result.

Concerning occupational status of the mothers, only 38 (26.4%) mothers were either private or government employees; the remaining 106(73.6%) were house wives.

Monthly income of the mother is less than 500 Birr/month in 68 (47.2%) cases, while 44 (30.6%) have an income between 500-1000 Birr/month, 16(11.1%) between 1001-1500 Birr/month, and the rest 16(11.1%) have income greater than 1500 Birr. Eleven (61.1%) HIV positive infants were born from mothers whose income is less than 500.00 birr/month.

The duration of labor for the mothers was less than 12 hours for 92(63.9%) cases, 37(25.7%) labored for >12 hours and the rest 15(10.4%) had no labor. Fourteen (77.8%) of HIV positive infants are born from mothers who labored for < 12 hours; Four (11.1%) were born from mothers who labored for > 12 hours.

Duration of rupture of membranes was less than 4 hours for the majority, 114(79.2%) and 30 mothers (20.8%) had rupture for greater than 5 hours. Four (22.2%) HIV positive infants were born from mothers who had rupture of membranes greater than 5 hours.

Twelve mothers (8.3%) didn't take any prophylaxis at all, sixty one (42.4%) mothers took single dose NVP, and 49

mothers (34%) took HAART. Seven (4.9%) took single dose NVP and AZT for < 1 month, 6(4.2%) received single dose NVP and AZT for > 1 month; nine (50%) HIV infected infants were born from mothers who took SD NVP and 33.3% of the HIV positive infants were born from mothers who took HAART.

Coming to neonatal prophylaxis, the majority of the neonates 93(64.6%) took only SD NVP, 23(16%) neonates took SD NVP + AZT for 1 week whereas 28(19.4%) neonates took SD NVP + AZT for 1 month. The majority of the HIV positive infants, 77.8% took SD NVP and the rest SD NVP and AZT.

Spontaneous vaginal delivery was the major mode of delivery, which constitute 111 (77.1%) of the cases. Three (2.1%) had instrumental delivery, 15 (10.4%) had emergency C/S and the rest 15(15%) had elective C/S. The majority of the HIV positive infants (83.3%) were delivered through SVD.

The majority of the mothers, 84(58.3%), chose exclusive replacement feeding, 50(34.7%) chose Exclusive Breast Feeding, 10(6.9%) chose Mixed feeding. From those who took Replacement Feeding only 10.7% were HIV positive, from those who took Exclusive Breast Feeding 12% were HIV Positive and from those who took mixed feeding, 30% were found to be HIV positive.

Twenty four (16.7%) mothers breast fed for < 4 months, 34(23.6%) mothers breast fed for 4 – 6 months, 2(1.4%) mothers breast fed for > 7 months and the remaining 84(58.3%) mothers didn't breast fed. From those who had replacement feeding, only 10.7% were found to be positive.

From a total of 144 mothers, 12 mothers had not received any prophylaxis during delivery; and of these, half of the children were exclusively breast fed & half were on exclusive replacement feeding. Only one infant was found to be HIV positive after receiving SD NVP & AZT for 1 month.

Sixty one mothers had received SD NVP whereby 19 opted for exclusive breast feeding, 36 for exclusive replacement feeding and 6 were practicing mixed feeding. From the exclusively breast fed infants , 17 infants received SD NVP and 2 became positive for HIV; two infants received SD NVP + AZT for a month and both were HIV negative. Of the infants who were put on exclusive replacement feeding, 35 of them were given SD NVP where 6 of them became HIV positive and 1 child received SD NVP + AZT for 1 month and was negative. From 6 infants who were on mixed feeding, one infant (out of 4) who received SD NVP was found to be positive, 2 infants received SD NVP + AZT for 1month and both were negative.

Thirteen mothers had taken SD NVP + AZT and five infants were on exclusive breast feeding, 7 were on exclusive replacement feeding and one was on mixed feeding. HIV Positive result was obtained from one infant out of three who had taken SD NVP & AZT for 1 month from the exclusively breast feeding population (one infant took SD NVP only & the other one SD NVP + AZT for 1 week & both were negative). All infants who were on Replacement feeding were all Negative / 2 were on SD NVP ,2 on SD NVP + AZT/ 1Month, 4 were on SD NVP + AZT 1 week/. One infant who received SD NVP + AZT for 1 month & put on mixed feeding was also negative.

From Mothers who had received SD NVP + with AZT/3TC for less than 1 month and using exclusive replacement feeding ,3 infants received SD NVP with AZT for a month & all were negative; 1 infant took SD NVP with AZT for 1 week & turned negative.

One mother was on exclusive breast feeding and infant had received SD NVP +AZT for 1 month & was negative.

A positive HIV test result was obtained from one infant who had received SD NVP + AZT for 1 month and put on mixed feeding.

Three mothers who had received SD NVP with AZT/3TC for greater than 1 month, one infant was put on exclusive breast feeding and two of them were put on exclusive replacement feeding, all infants received SD NVP + AZT 1week and all were negative.

A total of 49 mothers were already on HAART during pregnancy & delivery. Of these, 17 of their infants were on exclusive breast feeding, 30 were on replacement feeding and 2 infants were on mixed feeding. From the breast fed population, eleven infants were on SD NVP+ AZT 1Week & all were negative; 2 infants out of 6 who received SD NVP were HIV Positive. Three HIV Positive results were obtained from infants who received SD NVP from a total of 22 cases. Eight infants took SD NVP with AZT & all were negative for HIV. One infant out of two mixed breast fed cases turned positive after receiving SD NVP + AZT for 1 week (N.B the other one received SD NVP only).

Sixteen (88.9%) patients from a total of 18 HIV Infected individuals had one or more opportunistic infections; the commonest being oral candidiasis (32%), recurrent pneumonia and tuberculosis accounting for 24% of the cases each.

From the total 18 patients who were HIV Positive, 3(16.7%) died by the age between 15-18 months and 3 infants (16.7%) were lost from follow up. ART was ever started for 9 (50%) cases, 7 (38.9%) were not yet started during the study period and the status of the other 3 was not known since they were lost from follow up.

Discussions

In this study the overall prevalence of HIV Infection from infants who took either form of prophylaxis is 12.5%. This result is comparable to NVAZ Trial Taha 2003 [16] which states that rate of HIV Infection is 18.1% in infants who have taken prophylaxis at 6-8wks.

The sex distribution is comparable with a male to female ratio of 1:1.14. However, the rate of HIV Infection is greater in males (66.7%) as compared to females (33.3%).

The mean age for DNA PCR Diagnosis is 3.5months as compared to 45days that is recommended by the ministry of Health which helps to detect HIV Infection early; the delayed diagnosis in our case may be due to lack of awareness, or lack of access to facilities or short of diagnostic materials in the hospital itself.

From the HIV Positive cases only 27.7% of the total are either underweight or marasmic and the rest have a normal weight. This might be due to HIV Infection that has occurred during the peripartum period and patients are immunologically stable and not yet manifesting.

Fifty five point six percent of HIV positive infants were born from mothers who learnt for less than 8^{th} grade as compared to 44.5% of children born from mothers who learnt greater than 8^{th} grade, although not statistically significant. In addition, 61.1% of the HIV Infected cases were born from mothers with low socioeconomic status (<500 birr/month) which could be due to poor living standard leading to decreased tendency for health seeking behavior in the mothers that leads to poor ANC follow up. Thus, missed opportunity for early initiation of prophylactic treatment that would in turn increase the rate of mother to child transmission.

Neither the mode of delivery nor the duration of labor & rupture of membrane seem to affect the rate of positivity in this study in contrast to other studies which

suggest that instrumental deliveries, long duration of labor > 12 hours and rupture of membranes > 4hours is associated with increased risk of HIV Transmission [16]. This result might be due to the relatively small no of mothers who delivered other than SVD and small sample size as a whole used in this study.

When we see the maternal prophylaxis, the rate of HIV Infection is 8.3% in mothers who took no prophylaxis as compared to those who took either form of prophylaxis to prevent MTCT which is 12.9%, though not statistically significant.

From 4 infants born to mothers who took no prophylaxis, on exclusive breast feeding and received SD NVP with AZT for 1 month, 1(25%) turned reactive though not statistically significant. This percentage is higher as compared to the NVAZ Trial, Taha 2003 which states that the rate of HIV Infection is 15.3% at 6-8weeks [16]. The larger number in our case might be due to the small sample size that exaggerated the result.

Regardless of feeding options and history of maternal prophylaxis, the overall rate of HIV infection in patients who took SD prophylaxis is 15.1% and that of patients who took SD NVP with AZT 1 month or SD NVP + AZT for 1week is 7.8% implying a better efficacy in the combination treatment. These results are comparable to the Taha 2004 study in Malawi & Uganda: HIVNET 012 randomized trial which state that the rate of HIV Transmission is 16.9% for NVP and 6.5% for AZT+ SD NVP at 6-8weeks and 13.1% by age 14-16 weeks for SD NVP in the Ugandan study [15,16].

In cases where both mothers and infants took SD NVP the rate of HIV Infection in those who are exclusively breast fed is 11.8% as compared to those who were on exclusive replacement feeding which is 17.14%; though the difference is not statistically significant. This might suggest that SD NVP is comparably effective despite the different feeding options selected. This effect might be due to the extended half life of NVP up to 21 days that will result in decreased viral load in the first few weeks which is the time for maximum transmission of HIV through breast milk [13,14].This result is again comparable to HIVNET 012 study in Uganda which states that NVP demonstrates a persistent efficacy, 41 percent at age 18 months with the rate of infection being 15.7% in mothers who were exclusively breastfeeding for an average 9 months[16].

In mothers who had received SD NVP and practiced mixed feeding, 16.7% of the infants who received either form of prophylaxis turned positive. The increased percentage when compared to exclusive breast feeding may be due to the relatively increased risk of transmission that occurs with mixed feeding, though not statistically significant.

From mothers who took SD NVP with AZT as prophylaxis and opted for replacement feeding, all of the subjects were negative whether the infant had received SD NVP only or SD NVP with AZT of either 1 week or 1 month. But for those infants who were on exclusive breast feeding, one infant (33.3%) who received SD NVP with AZT for 1 month was positive which could probably be due to inadequate viral load suppression in the mother during delivery or might have acquired it during breast feeding.

From mothers who were on HAART, regardless of the feeding options chosen & infant prophylaxis, the rate of HIV Infection was 12.2% and 33.3% of the HIV Infected patients are born from mothers who took HAART. These percentages are higher than other studies done which state that the risk of HIV Infection is much lower in mothers who are on HAART [16]. This high rate of HIV Infection might be due to sub-optimal viral load suppression in the mothers that could occur as a result of poor adherence or

secondary to development of resistance (i.e. most of the HIV Positive infants are born from mothers who took HAART for greater than 6 months). ; From the HIV Infected infants born from mothers who took HAART, 83.3% were the ones who received SD NVP and 16.7% were the ones who received combination treatment (SD NVP + AZT for 1 week). This result might suggest that use of combination prophylaxis is much more effective than single dose treatment even in the face of maternal HAART.

From the breast feeding population, the majority, 27.8% of the HIV positive infants were breast fed for 4-6 months as compared to 5.6% in those who fed for greater than 7 months ; but the difference is not statistically significant.

When we see the outcome of the HIV Infected infants, 88.8% of the infants had one or more opportunistic infections but ART was started for only 50% of the patients & and 16.7% of the cases were dead before they celebrate their 2nd birthday.

From the above we suggest early diagnosis, treatment and follow up might be necessary to salvage their life. As the rate of HIV Infection in mothers on HAART is a much higher percentage as compared to other studies & further study should be done in this line. A large scale study involving every hospital in the capital & other regions of the country is recommended to evaluate the effect of the ART in Prevention of mother to child transmission.

Table 1 - Age and Weight Distribution of the Patients

Characteristics		Final HIV result		Total
		HIV negative	HIV positive	
Age of the child	1.5-4months	10(7.9%)	3(16.6%)	13(9.0%)
	5-9months	49(38.9%)	5(27.8%)	54(37.5%)
	10-14months	64(50.8%)	4(22.2%)	68(47.2%)
	15-19months	2(1.6%)	1(5.6%)	3(2.1%)
	20-24months	1(0.8%)	3(16.6%)	4(2.8%)
	>/= 25months	0(0%)	2(11.1%)	2(1.4%)
WEIGHT FOR AGE	Normal	114(90.5%)	13(72.2%)	127(88.2%)
	Under Weight	11(8.7%)	3(16.7%)	14(9.7%)
	Marasmus	1(0.8%)	2(11.1%)	3(2.1%)

[N.B. Age of the child is documented based on the age on their first appearance to the hospital. Percentages are calculated with in the final HIV test result.]

Table 2 Showing Socio-Demographic Status of the Mother versus Final HIV result of their Children

CHARACTERISTICS		Final HIV result of the children		
		HIV Negative	HIV Positive	Total
MATERNAL EDUCATIONAL STATUS	ILLITRATE	21(16.7%)	3(16.7%)	24(16.7%)
	< GRADE 8	39(31.0%)	7(38.9%)	46(31.9%)
	8 - 12 GRADE	35(27.8%)	3(16.7%)	38(26.4%)
	12 COMPLETE	24(19.0%)	2(11.1%)	26(18.1%)
	HIGHER EDUCATION	7(5.6%)	3(16.7%)	10(6.9%)
MONTHLY INCOME IN BIRR	<500	57 (45.2%)	11(61.1%)	68(47.2%)
	Between 501-1000	41(32.5%)	3(16.7%)	44(30.6%)
	Between 1001-1500	15(11.9%)	1(5.6%)	16(11.1%)
	Between 1501- 2000	6(4.8%)	0(0%)	6(4.2%)
	>2001	7(5.6%)	3(16.7%)	10(6.9%)
Occupation of the mother	Housewife	95	11	106
	Private worker	27	7	34
	Government employee	4	0	4

Table 3 Showing Maternal and Neonatal Prophylaxis as compared to Final HIV Result

Characters			Final HIV result		Total
			HIV negative	HIV positive	
Maternal Prophylaxis	No Prophylaxis	Count	11(8.7%)	1(5.6%)	12(8.3%)
	Single Dose NVP During Labor	Count	52(41.3%)	9(50.0%)	61(42.4%)
	AZT with SD NVP for <1 Month	Count	6(4.8%)	1(5.6%)	7(4.9%)
	AZT with SD NVP for >1Month	Count	6(4.8%)	0(.0%)	6(4.2%)
	AZT/3TC/SD NVP for < 1Month	Count	5(4.0%)	1(5.6%)	6(4.2%)
	AZT/3TC/NVP SD for >1Month	Count	3(2.4%)	0(.0%)	3(2.1%)
	HAART for <6 month	Count	15(11.9%)	1(5.6%)	16(11.1%)
	Mother on HAART for > 6 month	Count	28(22.2%)	5(27.8%)	33(22.9%)
Neonatal Prophylaxis	SD NVP only	Count	79(62.7%)	14(77.8%)	93(64.6%)
	SD NVP + AZT for 1 month	Count	20(15.9%)	3(16.7%)	23(16.0%)
	SD NVP + AZT for one week	Count	27(21.4%)	1(5.6%)	28(19.4%)

Table 4- Duration Of Breast Feeding As compared to Final HIV Result

			Final HIV result		
			HIV negative	HIV positive	Total
DBF2	< 4 months	Count	21	3	24
		% within Final HIV result	16.7%	16.7%	16.7%
	4-6 months	Count	29	5	34
		% within Final HIV result	23.0%	27.8%	23.6%
	> 7 months	Count	1	1	2
		% within Final HIV result	.8%	5.6%	1.4%
	No Breast Feeding (Replacement Feeding)	Count	75	9	84
		% within Final HIV result	59.5%	50.0%	58.3%
Total		Count	126	18	144
		% of Total	87.5%	12.5%	100.0%

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