HIV stigma limits the effectiveness of PMTCT in Guinea, the ANRS 12344 Diavina trial

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Context

Globally 45% of HIV-infected children are born in West and Central African countries where prevention of mother-to-child transmission (MTCT) programs are still limited [1]. The last revision of WHO guidelines included a reinforced HIV preventive therapy for infants at high risk of acquiring HIV that needs to be further investigated in the field [2].

In Guinea in 2013, among 7713 pregnant women presenting for delivery in university hospital (Ignace Deen, Donka) in Conakry, 87% reported no previous HIV testing. HIV test at delivery was widely accepted (98%) and HIV prevalence was 3,8% (IC 95% 3,2%-4,5%) whereas national prevalence was estimated at 1.7% (Solthis/PNLSH).

In 2015, according to national data, HIV testing is implemented in 297 PMTCT facilities, with a national coverage of 59%. Antiretroviral therapy (ART) coverage in pregnant mother is 88% (B+ option). Early infant diagnosis (EID) access remains low (11%) and only 47% of children with positive EID accessing to ART (PNLSH).

The 2016 WHO guidelines recommend reinforced ARV prophylaxis for infants at high risk of HIV MTCT that needs to be further investigated in the field [1].

Objective

Assess the operational efficacy of a strategy combining early infant diagnosis (EID) and reinforced preventive antiretroviral treatment from the birth[1] among infants at high risk of HIV infection[2].

[1] in a maximum of 48 hours after delivery

[2] born from HIV infected mothers who received less than 4 weeks of antiretroviral therapy prior delivery and / or with HIV infection diagnosed at delivery

Methods

Prospective non-comparative study of mother-child pairs with mother HIV-infected at high risk of MTCT in Ignace Deen Hospital, Conakry, Guinea.

Inclusion criteria

Mother-child pairs whose mother is HIV-infected and received less than 4 weeks of ART before delivery or whose HIV infection has been diagnosed at delivery.

Intervention

In Guinea, the national guidelines recommends HIV testing in all women in delivery room. In case of positive HIV infection screening from mother in the delivery room, ART (TDF/3TC/EFV) is immediately initiated. The participation of the study was presented to all **HIV-infected women who declare discovering HIV infection at birth and/or received less than 4 weeks of ART before delivery**. Potential participants provided written informed consent. They underwent screening evaluations, which included a medical history, a physical examination, laboratory confirmation of HIV status, complete blood count, HIV-RNA, CD4 cell count, creatinin, and ALT tests. Participants started the triple- ARV regimen at delivery. All women received trimethoprim-sulfamethoxazol (TMP/SMX) for prophylaxis of opportunistic infections. All infants received single dose NVP (2 mg/kg) immediately at birth and when the mother has signed the informed consent, **EID was performed and immediate reinforced ARV prophylaxis (AZT / 3TC / NVP) from birth for 12 weeks**. In case of positive result, ART (AZT / 3TC / LPV) was initiated as soon as possible.

TMP/SMX was given from 6 week of age until they were were confirmed to be HIV negative at 18 months.

Women were counselled to exclusively breastfeed for the first 6 months with complete cessation of breastfeeding at 12 months.

A psycho-social support was given during throughout the duration of the study by the psycho-social mediators from an association of PLHIV (Fédération Espoir Guinée).

The study provided the cost for transportation for scheduled or unscheduled visit, and participated to the cost for all outpatient and inpatient care required by participants while on study. ARV treatment were furnished by PNLSH.

Adverse events were graded according to the 1992 Adult and 1994 Pediatric toxicity tables of the Division of AIDS (DAIDS) and US National Institutes of Health (NIH).

Participants were followed for 72 weeks.

Virological testing

All laboratory testing was done at the INSP laboratory in Conakry. Plasma viral loads were quantified at delivery, 3, 6, 9, 12 and 18 months using the Generic HIV-1 RT-PCR assay (Biocentric, Bandol, France). EID was done at birth, at 14 weeks, at 6, 9 and 12 months of age using a home based technic based on Generic HIV-1 DNA assay (Biocentric, Bandol, France). HIV serology was performed at 9 and 18 months of age using rapid test (Alere Determine).

In September 2017, considering the high proportion of women considered at high risk for HIV transmission but with HIV-RNA<400 cp/mL at delivery, we analysed virological and pharmacological data in a subgroup of ten patients. Western blot HIV 1 and 2, HIV-1-RNA (Biocentric Generic HIV) were performed in the Virology laboratory of Necker Hospital (Paris, France). ARV plasma concentrations were assessed in the Pharmacology laboratory of Bichat Hospital (Paris, France).

In December 2017, considering concern about EID quality, blood samples were transferred in the virology laboratory at Necker Hospital in Paris, France. In April 2018, considering concern about EID results (false positive), GenXpert HIV qual (Cepheid) was used and performed in the virology laboratory at Donka Hospital in Conakry, Guinea.

Quantitative and qualitative data on non disclosure HIV status and stigma

We performed a quantitative sub-study of 40 women included in the trial to assess the factors associated with misclassification of MTCT risk. Miclassification of MTCT risk was defined by women declaring to be newly diagnosed with HIV and/or to have received ARV for <4 weeks but having plasma HIV-1-RNA <400 copies/mL at delivery. Correct classification of MTCT risk was defined by women declaring to be newly diagnosed with HIV and/or to have received ARV for <4 weeks but having plasma HIV-1-RNA >400 copies/mL at delivery. Stigma and auto stigmatisation was evaluated by psycho-social mediators based on direct interview and phone call.

Statistical analysis.

Chi-2 and Fisher exact tests were used.

Results

From Feb 2017 to Feb 2018, 6,493 women were admitted for delivery, 6,141 (96%) accepted HIV testing, 114 women were HIV-infected (1.9%), all were infected with HIV-1 and 57 were considered at high risk of MTCT based of mother interview at the delivery room . Overall 51 women and 56 children were included (3 maternal or neonatal deaths, 3 refusal).

Table 1. Characteristics of the 51 women at inclusion

Features	
Reasons for considering mothers at high risk of MTCT (n, %)	
- women declaring to know their HIV status but to have received < 4 weeks of ART before delivery	13 (25%, CI95% 14-37%)
- women declaring to be newly diagnosed with HIV at delivery	38 (75%, CI95% 63-86%)
Age (median, IQR) (years)	30 (26-36)
CD4 (median, IQR) (/mm3)	411 (315-590)
Proportion of mothers with HIV-RNA<400 cp/mL at delivery, n (%, CI95%): -among all subjects with available results of HIV-RNA at delivery -among those with known HIV status but short duration of ART (0 – 4 weeks) before delivery -among those declaring to discover HIV status at delivery	 23/48 (48%, CI95% 34-62%) 8/13 (61%, CI95% 35-88%) 15/35 (42%, CI95% 26-59%)

Table 2. Virological and pharmacological characteristic of women with HIV-RNA <400 cp/mL at inclusion (n=10)

	N°	WB positif	HIV-RNA (cp/mL)	ARV plasma concentration (ng/mL)					
				EFV	AZT	FTC	3TC	NVP	TDF
HIV diagnosed at delivery	1	VIH-1	<400	180		< 10			21
	2	VIH-1	<400	3646		466			59
	3	VIH-1	<400	2393		39			69
	4	VIH-1	<400	737		14			46
	5	VIH-1	<400	167		< 10			31
	6	VIH-1	<400	834		82			51
HIV-infected, no ART	7	VIH-1	<400		67		331	9271	
	8	VIH-1	<400	2733		209			216
	9	VIH-1	<400		6		87	6173	

Table 3. Factors associated with factors associated with misclassification of the MTCT risk

	Misclassification of MTCT risk: maternal HIV-RNA <400 copies/mL at delivery N=21	Correct classification of MTCT risk: maternal HIV-RNA <400 copies/mL at delivery N=19	p
Single	**5%**	**32%**	**0.04**
Never attended school	19%	37%	ns
Poor understanding of protocol	10%	26%	ns
Motivation to participate in the study			
Best treatment to protect child	33%	58%	ns
Benefit from EID	19%	26%	ns
Better medical care for mother	**43%**	**5%**	**0.01**
Free healthcare	0%	5%	ns
Main concerns about HIV care in hospital			
Difficulties to talk about HIV	67%	47%	ns
Fear of lack of confidentiality	29%	42%	ns

Table 4. Adverse event and haematological tolerance of reinforced ARV prophylaxis in children

adverse event		
Number of children presenting adverse event	37/56 (66%)	
Number of children presenting serious adverse events	12/56 (21%)	
Number of children presenting adverse events (except anaemia) related to reinforced ARV prophylaxis	0/56 (0%)	
Haematological tolerance of reinforced ARV prophylaxis	At Week 4	At Week 8
No. of children with available results of haemoglobin measures (n, %)	46 (82%)	45 (80%)
Haemoglobin level (median, IQR) (g/dL)	10.0 (9.5; 10.5)	9.5 (8.5; 11.0)
Iron supplementation prescribed/indicated (n, %)	10/10 (100%)	11/6 (>100%)*
Variation of haemoglobin levels between 4 and 8 weeks of age (median, IQR)	-0.5 (-1.5; +0.2)	
No. of children with anaemia requiring iron supplements at 4 and/or 8 weeks of age n (%, CI95%)	16/46 (35%; CI95% 21-49%)	
No. of children with anaemia requiring AZT interruption at 4 and/or 8 weeks of age (n, %)	0 (0%)	

*Note: 5 children with Hb levels between 8.5 and 9 g/dL also started iron supplement (probably not understanding the different anaemia management guidelines between S4 and S8).

Table 5. Comparison of the clinical and virological outcome of women at high and low-risk of MTCT (based on the results of HIV-RNA at delivery)

	High risk of MTCT (HIV-ARN>400 cp/mL at delivery) N=25	Low risk of MTCT (HIV-ARN< 400 cp/mL at delivery) N=23	Total (Undetermined risk of MTCT HIV-ARN not available at delivery n=3) N=51	p
Death n (%)	0/25 (0, CI95% **0**-12%)	1/23 (4%, CI95% 0-13)	1/51 (2%, CI95% 0-6%)	ns
Virological failure (>400 cp/mL) n (%, CI95%)	5/16 (31%, CI95% 8-54)	10/22 (45%, CI95% 25-66)	17/40 (43%, CI95% 27-58%)	ns
Lost follow-up at delivery, n (%, CI95%)	6/25 (24%, CI95% 7-41)	1/23 (4%, CI95% 0-13%)	8/51 (16%, CI95% 6-27%)	ns
Lost of follow-up between delivery and Week 72 , n (%, CI95%)	**13/25 (52%, CI95% 32-72)**	**4/22 (18%, CI95% 2-34)**	**19/50 (38%, CI95% 26-51%)**	**0.03**

Table 6. Comparison of the clinical and virological outcome between children at high and low-risk of MTCT (based on the results of their maternal HIV-RNA at delivery)

	High risk MTCT children (maternal VL >400 cp/mL at delivery) N=27	Low risk MTCT children (maternal VL<400 cp/mL at delivery) N=26	Total N=56	p
Death n (%, CI95%)	2 (7%, CI95% 0-17%)	2 (8%, CI95% 0-18%)	4 (7%, CI95% 0-14%)	
Lost of follow-up at birth, n (%, CI95%)	6/27 (22%, CI95% 7-38%)	*1/25 (4%, CI95% 0-12%)*	*8 (14%,* CI95% *5-23%)*	ns
Lost of follow-up between birth and Week 72 , n (%, CI95%)	**12/25 (48%,** CI95% **28-68%)**	**2/24 (8%,** CI95% **0-19%)**	**16/48 (33%,** CI95% **20-47%)**	**0.004**
EID collected and reinforced ARV prophylaxis **prescribed** at birth, n (%, CI95%)	23/27 (85%, CI95% 72-99%)	23/26 (88%, CI95%76-100%)	48 (86%, CI95% 85-100%)	ns
Completion of 12 weeks reinforced ARV prophylaxis, n (%, CI95%)	**16/25 (64%, CI95% 45-82%)**	**23/24 (96%, CI95% 88-100%)**	**41/52 (79%, CI95% 68-90%)**	**0.01**
HIV infection diagnosed at birth, n (%, CI95%)	3/18 (17%, CI95% 0-34%)	0/24 (0%, CI95% 0-13%)	3/44 (7%, CI95% 0-14%)	ns
HIV infection from birth to 18 months, n (%, CI95%)	**4/15 (27%, CI95% 4-49%)**	**0/22 (0%, CI95% 0-14%)**	**4/37 (11%, CI95% 1-21%)**	**0.02**

Table 7. Reasons associated to lost of follow-up in children

Causes	N	p
Stigma/auto-stigma	**11**	
Economic Constraints	2	**p=0,002**
Travels	3	

Conclusions

These results highlight the value of HIV testing at delivery since a quarter of HIV-infected women discovered their infection at delivery. This could be even more useful in rural areas where PMTCT program are less implemented. Early infant diagnosis at birth and reinforced ARV prophylaxis seems feasible, and tolerance of 12 weeks of reinforced ARV prophylaxis AZT containing regimen is acceptable even in one third of children will need iron supplementation.

However, the risk of MTCT was overestimated in our study, leading to unnecessary reinforced neonatal prophylaxis, because of the lack of disclosure of HIV and/or ART status to caregivers, which does not appear to be related to a misunderstanding or to indirect benefits of the protocol. Furthermore the high proportion of high-risk women who want better treatment for their child and the low-risk women who want the best care for themselves shows a good understanding of the strategy. Non disclosure or HIV status or ART intake has been previously reported in 5-20% of people entering HIV programmes, particularly among pregnant women in sub-Saharan Africa [3-5]. This higher rate of non disclosure observed in our study could be linked to the high level of HIV stigma observed in Guinea [1] and to the fear of HIV disclosure, main barriers to PMTCT in Africa [6].

Quantification of maternal HIV-RNA near delivery seems crucial to adequately estimate the risk of MTCT and therefore adapt the neonatal prophylaxis accordingly.

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