HIV genotype and drug resistance profile in vertically infected children

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Background

The availability and timely administration of combination anti-retroviral therapy (cART) has not only reduced the rate of mother-to-child transmission (MTCT), but also improved the prognosis of HIV-infected newborns. However, one of the main concerns in HIV-infected children is drug resistance (*DR*).

- *selected DR* (= *sDR*) may arise from suboptimal adherence and dosing;
- *transmitted DR*-HIV (= *tDR*) may originate from MTCT and increase the risk of *sDR*

OBJECTIVE:

to evaluate the frequency of sDR and tDR in HIV vertically infected children in Switzerland

Patients and methods

We performed a retrospective analysis of prospectively entered data of HIV transmission in mother-child (MoC) pairs of the Swiss Mother-Child HIV (MoCHIV) cohort.

- *tDR* was identified by HIV-*DR* genotypes in MoC pairs or in newborns directly *after* birth.
- *sDR* was identified by HIV-*DR* genotypes emerging at available follow-up visits to define new *DR* mutations (DRM).

DRM genotypes were determined by Sanger sequencing on amplicons generated from HIV RNA in plasma (N=66) and from proviral DNA in PBMCs (N=43).

Data on HIV load, CD4+ T-cell count, cART, adherence, and clinical information were obtained from the SHCS data base

Population

We identified 22 MoC pairs.

Nearly all mothers (95.5%) were treatment-naïve before pregnancy and only 50% had received any kind of ART (cART in 54.5%) during pregnancy or at delivery (***Fig 1***).

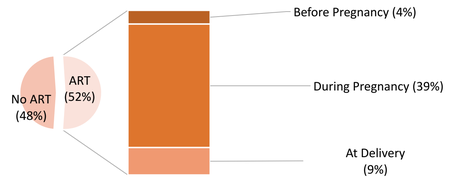

Fig 1. **Summary of ART exposure in mothers or newborns**

Results 1:

- Follow-up 15 years (median, IQR 12-18, range 0-26).
- HIV subtype-B was found in 59% (13/22), being concordant in all MoC pairs (***Table 1***).
- HIV-*sDR* was identified in 63.6% (14/22)
- 4 out of 14 (28.6%) children with HIV-*sDR* were treatment-naïve at time of the emergence of first DRM.

	TOTAL=22	With sDR=14	Without sDR=8
Gender (female)	11 (50%)	7 (50%)	4 (50%)
HIV subtype (B)	13 (59%)	9 (64.2%)	4 (50%)
GE (median)	39	38	37.5
Mother therapy (yes)	1 (4.5%)	0	1 (12.5%)
Antenatal prophylaxis (yes)	8 (36.4%)	6 (42.8%)	2 (25%)
In utero exposure (time in days)	55	51	66
Nadir CD4 Tcells (mean)			
cells/mmc	396	341	493
%	24.5	19	25
Zenith VL (copies/ml)	927957	1228403	402176
ART child (start < 3 mths)	12 (54.5%)	7 (50%)	5 (62.5%)
ART changes (times)	5.8	6.9	4

***Table 1. Comparison between children with and without HIV-*sDR.**

Results 2:

- The number of ART changes during paediatric lifetime was greater in those with HIV-*sDR* (6.9x *vs.* 4x), but early ART (<3 months of age) was protective against HIV-*sDR* (50% vs. 62.5%;p=0.56).
- HIV-*sDR* was associated with lower CD4+ T-cell counts, but not with peak HIV plasma load (***Fig 2***).

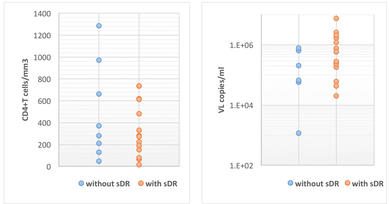

Fig. 2. **Nadir of CD4+T cells counts (left) and peak HIV load (right) in children with or without HIV-*sDR* during follow up.**

Results 3:

- HIV-*tDR was identified* in 1/22 (4,5%)
- HIV-*tDR* was associated with early emergence of sDR (0.83 vs 3.5 years; p>0.05)
- HIV-*tDR* was associated with higher rate of sDR (100 vs 61.9%; p>0.05)(***Table 2***).

	TOTAL	With tDR	Without tDR
Gender (female)	11 (50%)	1 (100%)	10 (47.6%)
HIV subtype (B)	13 (59%)	1 (100%)	12 (57.1%)
Gestational age (median)	38	42	38
Mother therapy (yes)	1 (4.5%)	0	1 (48.1%)
Antenatal prophylaxis (yes)	8 (36.4%)	0	8 (38.1%)
In utero exposure (mean time in days)	55 days	0	55
sDR	14 (63.6%)	1(100%)	13 (61.9%)
Median age at first sDR on tot n°14 children (in years)		10m (0.83)	3y 6m (3.5)

***Tab 2. Comparison between children with and without HIV-*tDR.**

Results 3:

- The number of major HIV-DRM ranged from 1 and 8
- 5 children had more than 2 cumulative HIV-DRMs
- M184V was most frequently detected (22,7%) (***Fig 3***).

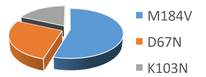

Fig 3. **Most frequently detected major HIV-DR mutations.**

Conclusions

- The rate of HIV-*tDR* (4.5%) in the Swiss MoCHIV cohort is lower than in other studies, but still within the previously described range.
- HIV-*tDR* was followed by early *sDR* mutations, but the low overall number precluded further analysis.
- The rate of HIV-*sDR 63.6%* and nearly half of the children (28.6%) were treatment-naÏve pointing to important opportunities/challenges for improving HIV cART management.
- Higher number of ART changes correlated with HIV-sDR changes.
- Current sequencing data indicate that HIV-*tDR* played only a minor role in HIV-DRM emergence.
- Next generation sequencing approaches may be required to ensure that relevant minority species of HIV-DRM pre-existing in the mothers may not have been overlooked.

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