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Antiretroviral therapy with indinavir 400 mg-ritonavir 100 mg twice daily containing regimen in HIV-1 infected pregnant women

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Abstract

Background:
IDV/RTV is a simple, potent, well tolerated regimen in HIV patients (pts).Whether this regimen could be safely used in pregnant women remains to be determined.

Objectives:
To evaluate the safety and efficacy of IDV/RTV based therapy in HIV pregnant women

Methods:
An observational study including pregnant women attending our unit and receiving a IDV/RTV containing-regimen. Plasma HIV-1 RNA, CD4 count, chemistry, Cmin plasma IDV and RTV were measured and adverse effects recorded monthly until delivery.

Results:
Thirty-two women received an antiretroviral therapy (ART) with IDV/RTV (400/100 mg bid) and a backbone of AZT-3TC (n=30), D4T-3TC (n=1), AZT-DDI (n=1). At baseline, the first visit during pregnancy, the median (med) term was 9 weeks, med age was 32 years. Twenty-one pts were on ART with14 receiving IDV/RTV for a med of 9 months (1-16). For the 11 ART naïve, the med time of RTV/IDV initiation was 20 weeks of gestation (3-30). For these 11, med baseline HIV RNA was 9265 cp/mL(261-50.800), CD4 count was 193/µL (112-395).
Med exposure to IDV/RTV during pregnancy was 24 weeks (5-40). In 4/32 pts IDV/RTV was discontinued before delivery, 1 for virological failure and 3 for intolerance: 2 xerosis and 1 ingrowing toenail. No nephrolithiasis, grade 2 hyperbilirubinemia, hyperglycemia or elevated creatinine were observed.
Median Cmin was 208 ng/mL(0-10665) for IDV in the third trimester .(n=27), one pt was overdosed for IDV and one non-observant.
At delivery, 28/31 (90%) had an HIV-RNA <400cps/mL., the 3 detectable value: 1200, 1870 and 3100 cps/ml were related to pts poor adherence.
The pregnancies ended with one spontaneous miscarriage at 11 weeks and the birth of 33 infants (2 set of twins). Mode of delivery was vaginal for 12 pts, elective caesarian section (cs) for18 and one emergency cs. Med term of delivery was 38 weeks (33-42) with premature delivery <37 weeks in 4/31 pts.
None of the 32 infants reaching 3 months was infected using HIV-RNA and DNA PCR. The med birth-weight was 3000g (2100-4600), 5 were hypotrophic including 3/4 twins(1600-2500 g). At 4 days, med hb was 14g (10.4-18.7), med bilirubine 115 (14-223), SGOT 45 (22-71) all within the normal range.

Conclusion: At delivery, 90% of pregnant women assigned to IDV/RTV containing ART showed an undetectable plasma HIV-RNA with an overall adequate IDV Cmin and good tolerance for the mothers and infants suggesting that this simple boosted PI regimen could be used in HIV pregnant women.

Background

- In our institution, specific multidisciplinary care including: obstetrics and gynecology, pediatrics,virology, infectious and internal medecine,pharmacology,psychiatric and social workers units are provided to HIV pregnant women and their infants.
- The objective of antepartum therapeutic intervention is to target the lowest viral load (VL) during the last trimester of pregnancy until delivery to protect the neonates from HIV transmission and to preserve future therapeutic options for the mother .
- This efficacy objective must be balanced with the potential toxicity of any antiretroviral therapeutic regimen .
- The use of HAART regimen containing protease inhibitor during pregnancy is common in our experience and is now recommanded in the french guidelines.(2004)
- among the HIV Protease inhibitors : Indinavir (IDV) has the best profile in term of protein binding and lipid solubility to allow optimal tissues and secretions diffusion .
- Boosted IDV with ritonavir (RTV) results in a reduction of dosing schedule, number of pills, dietary restriction and results in an increase of the IDV AUC and trough plasma concentration (Cmin).
- IDV/RTV 400/100 mg bid has been evaluated with satisfactory results in term of efficacy, adherence and tolerability in naive and experienced HIV infected patients.

C. Duvivier – Antiviral therapy 2003 ; 8:603-609
J. Ghosn – AIDS 2003 ; 17:209-214

Objectives

•The aim of this study is to assess the risk-benefit balance of IDV/RTV containing regimen during the antenatal period in HIV pregnant women and their infant.

Patients and Methods

- 32 consecutive HIV-1 infected pregnant women were included in this observational single center non comparative study from september 2002 to october 2003 and all born infants have completed their 6 months visit .
- Women were followed monthly with plasma HIV-1RNA (VL), CD4, chemistry. plasma IDV and RTV C.min were performed during the last trimester of pregnancy.
- The mode of delivery was determined comprehensively according to the last VL , the woman obstetrical history and personal decision.
- All women received Zidovudine (ZDV) infusion during labour and babies received 6 weeks ZDV (0.2 mg /Kg x 4 /day) as recommanded in the french guidelines.
- None of the women did breastfeed their children .

Baseline characteristics of women (n = 32)

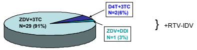
Median age (years)	32 [20- 43] years
Origin	84% from sub-saharian Africa
Gestational age at entry (weeks)	14 [1-31]
Median Viral Load (copies/ml)	992 [200-140.000]
Median CD4 (cells/mm3)	335 [147-828]

11 ART naive (34%) → starting ARV at 20 weeks of gestation [3-30]

21 ART experienced
- 14 with an ongoing RTV-IDV regimen for a median time of 9 Months [1-16] at entry
- 7 pretreated with: ZDV+3TC(n=2), ZDV+3TC+NFV(n=2, ZDV+3TC+TDF(n=1), ZDV+3TC+SQV/rtv (n=1), DDI+3TC+TDF (n=1)

Drug exposure during pregnancy

All Regimen included two nucleoside reverse transcriptase inhibitors and ritonavir 100mg+indinavir 400mg twice daily



Median exposure to RTV / IDV (in weeks)

- **Total** : **n = 32 : 24.4 w** [5 - 39.9]
- Naive ART : n = 11 : 20.9 w [6 - 36.3]
- Prior ART : n = 21 : 30.9 w [5 - 39.9]

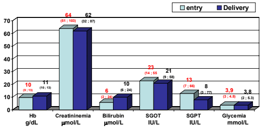
Safety : mothers (1)

- **27/31 (87%) completed their pregnancy on RTV / IDV**
- **Reason for discontinuation : n = 4**

- **1 virologic failure** (W8 RTV/IDV) ➔ switched for LPV/RTV
- **1 liver enzyme elevation** : SGOT rise from 25 to 140 IU/L (W16 RTV/IDV) ➔ switched for NFV
- **1 xerosis** (W12 RTV/IDV) ➔ switched for NFV
- **1 xerosis + ingrowing toenail** (w10 RTV/IDV) ➔ switched for LPV/RTV

- No nephrolithiasis observed

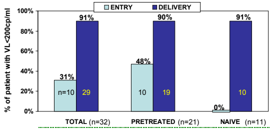
Safety: mothers (2)
Median (range)



Efficacy

- plasma HIV-1 RNA < 400 cp/ml at delivery or outcome
  - 29/32 = 91 % (ITT)
  - 10/11 naive
  - 19/21 pretreated
- 3 patients presented VL > 400 cp/ml (1200 / 1870 / 3100 cp/ml)
  - 2/3 with IDV Cmin < LOQ
  - and one IDV Cmin = 89 ng/ml related to adherence difficulties.
- Median CD4 at delivery : 352 /mm³ [113-948]
- None of the 33 born infants are HIV infected :RNA and DNA HIV1-PCR neg at birth, 3 and 6 months .

Viral load and CD4 evolution between entry and delivery



	TOTAL entry	TOTAL delivery	PRETREATED entry	PRETREATED delivery	NAIVE entry	NAIVE delivery
Median VL log (range)	3 (2,3 ; 5,15)	2,3 (2,3 ; 3,5)	2,3 (2,3 ; 5,15)	2,3 (2,3 ; 3,5)	3,98 (2,42 ; 4,71)	2,3 (2,3 ; 3,08)
CD4/mm³ (range)	335 (112 ; 828)	352 (113 ; 948)	366 (147 ; 828)	402 (113 ; 828)	193 (112 ; 395)	273 (125 ; 706)

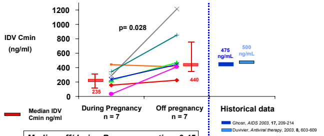
Indinavir pharmacokinetics

- Trough plasma concentrations (Cmin) of IDV and RTV were determined by high performance liquid chromatography (HPLC) coupled with UV detection as previously described [*Woolf et al, 1995, Marsh et al 1997*].
- IDV and RTV Limits of quantification (LOQ) = 5 and 30 ng/ml, respectively.
- Data available during pregnancy (last trimester) for 28 patients,
- Data available during pregnancy and off pregnancy for 7 patients,

•Median (range, n) IDV Cmin = 162 ng/ml [5- 4852] n= 28,

- 4/28 IDV Cmin were < LOQ
- Among the 3 patients with a VL > 400 cp/mL at delivery :
  - 2 Cmin were < LOQ
  - and the third one was low with 89 ng/ml refelecting adherence difficulties.

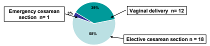
IDV C_{min} during and off pregnancy in 7 patients treated with IDV/RTV (400/100 mg bid) containing regimen



Median off/during Pregnancy ratio = 0.45

Pregnancy outcome

- **Mode of delivery for 31 women**
- **33 infants born (2 twins pairs)**



➔ **1 spontaneous miscarriage,** at 11 weeks of gestation after 5 weeks on RTV/IDV containing regimen

➔ **Gestational age at delivery (n=31)**
- Median : 38 weeks [33- 42]
- 4 ≤ 37 weeks (including 1 twins pair)
- 0 < 32 weeks

Infants status at birth
(n = 33)

•Median gestational age	38 weeks [33- 42]
•Median birth weight	3 000 g [2100-4600]
•Intra uterin growth retardation : birth weight below 10th percentile *(French guidelines)*	n = 5 including 3/4 twins
•Cranial perimeter	no microcephalia (below 5 th percentile)
•Apgar score : < 7 at 5 mn	n = 1/33 (36.5 weeks)

Clinical examination was normal for all of the 33 newborn

Toxicity: at 4 days and 1 month of age in infants
Median, [range] n = 33

	Infant Day 4 median [range]	Infant M1 median [range]
Hemoglobinia g/dl (normal range :14-22)	13.4 [10.4-17.5]	9.9 [8.3-13.9]
Neutrophilia /mm3 (normal : 4000-22000)	3993 [920- 9500]	1756 [773- 3825]
Total bilirubin µmol/l (normal range < 250)	104 [14-194]	15 [4- 28]
SGOT UI/ ml (normal < 60)	46 [22- 69]	35 [23-87]
Creatininemia µmol/l (normal: 18-88)	53 [37-67]	33 [14- 56]
Lactatemia mmol/l normal < 3	Not applicable	3.1 [1.4- 6.4]

Conclusion

- IDV / RTV containing regimen appears to be safe and potent in mothers and infants.
- The IDV Cmin is reduced during the last trimester of pregnancy when compared to non pregancy data with no deleterious effect on viral load .
- No renal toxicity or hyperbilirubinemia was observed in infants at birth and at one month .
- This simple low cost boosted PI regimen might be an alternative during pregnancy in countries with limited ressources.
- **These encouraging preliminary data deserve confirmation in prospective largest studies .**

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