The Impact of Isoniazid Preventive Therapy and Antiretroviral Therapy on Tuberculosis Incidence in Children Living with HIV in Vietnam

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TB, HIV, and IPT

- People co-infected with HIV and tuberculosis (TB) are at higher risk of developing active TB.
- Isoniazid preventive therapy (IPT) reduces risk of TB in HIV+ persons (~70% in children).
- IPT for HIV infected adults and children was recommended by Vietnam's Ministry of Health in 2009.
- The WHO subsequently released their guidelines on Intensified Case Finding and IPT for people living with HIV in May 2011, which provided further support for this approach in resource-limited countries.

Zar, *BMJ* 2006

TB, HIV, and IPT in Vietnam

- However until early 2011, IPT was not being routinely provided to HIV+ children in Vietnam.

- To address this gap, in July 2011 Ho Chi Minh City Pediatric Hospital #1 (Peds 1) collaborated with Clinton Health Access Initiative (CHAI) to pilot a pediatric IPT program for HIV+ children at the outpatient clinic (OPC) in Peds 1, the largest pediatric HIV OPC in Vietnam.

Overview of IPT

- HIV patients at Peds 1 OPC were screened for IPT eligibility by questioning for symptoms of TB
  - cough, fever, weight loss/no weight gain & TB contact
- Those with symptoms were investigated for TB
- All without TB after screening/investigations were offered IPT if no other contraindications to INH
  - (active/chronic hepatitis, ALT > 3x ULN, peripheral nerve diseases)
- Treatment included 6 months of isoniazid and vitamin B6 supplementation, with monthly follow up during treatment and screening for TB at each visit

Overview of IPT assessment

- Objectives
  - to explore the impact of IPT and antiretroviral therapy (ART) on incident active TB disease in HIV+ children
  - to determine the safety and tolerability of IPT in HIV+ children.
- Retrospective observational study by review of health records of patients registered at Peds 1 during study period of July 2009 – June 2013
- Period of study: 2 phases
  - Pre-IPT: 2 years prior to IPT introduction: 07/2009 – 06/2011
  - Post-IPT: 2 years after IPT introduction: 07/2011 – 06/2013

Overview of IPT assessment (cont.)

- Target population
  - All HIV patients managed by Peds 1 from July 2009 to June 2013, including exits (deaths, transfer-out, LTFU) in this period. All patients on ART and pre-ART are all included.
- Method of data collection:
  - Retrospective review of outpatient records and inpatient records (for TB suspected cases hospitalized after IPT initiation)

Overview of IPT assessment (cont.)

- Data collection includedd
  - –date of birth
  - –date of registration and ART initiation
  - –history of TB disease anytime during follow-up
  - –date and results of initial IPT screening
  - –IPT treatment history including liver enzyme test results
  - –exits from Peds 1 program with reason for exit
    - death, transfer, lost to follow-up

Analysis

- Descriptive statistics:
  - IPT initiation/discontinuation rates
  - IPT side effects rates
  - TB incidence rates pre- and post-IPT treatment
  - Incidence rate ratios for TB incidence pre- and post-IPT treatment and pre- and post-ART.

- Poisson regression was performed to calculate incidence rate ratio (IRR) of TB based on IPT status adjusted for the effects of age, CD4, and ART

Cohort Characteristics

Characteristics of 854 children in study	
Female sex	418 (48.9%)
Age at study start (July 1, 2009)	
<1 year	127 (14.9%)
1 – <2 years	78 (9.1%)
2 – <5 years	273 (32%)
5 – <10 years	309 (36.2%)
10+ years	67 (7.8%)
Degree of immunodeficiency at ART initiation	
Severe	631 (73.9%)
Advanced	109 (12.8%)
Mild/ Not significant	114 (13.3%)
Initiated ART during follow-up	762 (89.2%)
Initiated IPT during follow-up	581 (68.0%)
No ART before or after IPT	29 (3.4%)
Initiated ART before IPT	525 (61.5%)
Initiated ART after IPT	27 (3.2%)

Results – IPT uptake

# of patients managed at Peds 1 during study period (Jul 2009 – Jun 2013)	N=854	
# of patients screened for IPT	**582**	**68.1%**
+ # of patients with negative TB screening	**578**	**99.3%**
+ # of patients with positive TB screening & referred to TB sites	**4**	**0.7%**
- # of patients diagnosed TB (+) and initiated anti-TB tx	**1**	**0.2%**
- # of patients with TB (-)	3	0.5%
# of eligible patients ever initiated IPT	**N = 581**	
+ # of patients currently on IPT	**12**	**2.1%**
+ # of patients completed IPT	**551**	**94.8%**
+ # of IPT discontinuers	**18**	**3.1%**

Results – IPT uptake

# of patients managed at Ped 1 during study period (Jul 2009 – Jun 2013)	N=854	
# of patients ever initiated IPT	581	68%
# of patients at Ped 1 not started IPT yet	113	13%
# patients exited before IPT initiation (including transfer out, LTFU and deaths)	160	19%
+ # of patients transferred out	69	8%
+ # of patients died	54	6%
+ # of patients LTFU	37	4%

IPT discontinuations

Total discontinuations	18/581 (3.1%)
Reasons for discontinuation	
INH side effects	6 (1.0%)
TB disease diagnosed	1 (0.2%)
Death	1 (0.2%)
Caregiver choice	7 (1.2%)
Loss to follow-up	2 (0.5%)
Transfer out and stopped	1 (0.2%)

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Caregiver choice	7 (1.2%)
Loss to follow-up	2 (0.5%)
Transfer out and stopped	1 (0.2%)

- 6 stopped IPT due to INH-side effects:
  - 1 vomited
  - 1 rash/hypersensitivity
  - 4 increased liver enzyme - 3 with ALT increased <2 times at baseline
- 32 patients (5.5%, n=581) with ALT increased < 2x ULN, 3 of whom (9.4%, n=32) stopped IPT due to INH side effects

TB diagnoses

- During the 4-year period, 54 TB cases were diagnosed amongst 854 children during 2220 patient-years of follow-up (PY)
  - 51 cases pre-IPT and 3 after IPT initiation (post-IPT)

- No TB cases were detected among patients who had completed IPT (median 16 months post-completion).

TB diagnoses – post-IPT

- 3 developed TB after IPT initiation
- 1 case diagnosed while on IPT:
  - **Case 1:** ART initiation with CD4:17. Started IPT after 1 mth on ART. Diagnosed with TB lymphadenitis 2 mths after IPT initiation with abdominal pain, swollen abdomen and nausea.
- 2 patients who stopped IPT for liver enzyme elevation, but then died of suspected TB soon after discontinuation
  - **Case 2:** ART initiation with CD4: 2. Hospitalized due to anemia, pneumonia and pulmonary lymph nodes 1 mth before IPT. Stopped IPT after 3 wks due to increased liver enzyme. Diagnosed with pulmonary TB with swollen abdomen, wasting and died.
  - **Case 3:** Initiated ART and IPT on the same day. CD4: 0.5%. Stopped IPT after 2 weeks due to increased liver enzyme. Diagnosed of pulmonary TB and died after 2 months.
- **All 3 cases – advanced HIV disease, IPT started with or soon after ART**

Incidence rates & incidence rate ratios for TB by treatment category

	Person-years	TB	Incidence rate per 100 PY (Mid-P 95% CI)	Crude Incidence Rate Ratio (IRR) (Mid-P 95% CI)
Pre-IPT	1235.3	51	4.13 (3.11–5.39)	REF
Post-IPT	985.3	3	0.30 (0.077–0.83)	0.074 (0.018–0.21)
Total	2220.6	54	2.43 (1.85–3.15)	n/a

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Post-IPT	985.3	3	0.30 (0.077–0.83)	0.074 (0.018–0.21)
Pre-ART	211.6	20	9.45 (5.94–14.34)	REF
Post-ART	2009.0	34	1.69 (1.19–2.34)	0.17 (0.096–0.29)
Total	2220.6	54	2.43 (1.85–3.15)	n/a

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Pre-ART	211.6	20	9.45 (5.94–14.34)	REF
Post-ART	2009.0	34	1.69 (1.19–2.34)	0.17 (0.096–0.29)
No therapy	166.8	20	11.99 (7.53–18.19)	REF
IPT only	44.8	0	n/a	n/a
ART only	1068.5	31	2.90 (2.00–4.07)	**0.24** (0.14–0.43)
Both ART & IPT	940.6	3	0.32 (0.081–0.87)	**0.027** (0.006–0.082)
Total	2220.6	54	2.43 (1.85–3.15)	n/a

Poisson regression of TB cases – controlling for age, HIV severity

	Univariate		Multivariate	
	IRR (95% Wald CI)	p-value	IRR (95% Wald CI)	p-value
Age at follow-up				
<1 year	1		1	
1 – <2 years	0.274 (0.103 – 0.728)	0.009	0.242 (0.084 – 0.695)	0.008
2 – <5 years	0.196 (0.099 – 0.388)	<0.001	0.255 (0.126 – 0.514)	<0.001
5 – <10 years	0.098 (0.048 – 0.203)	<0.001	0.154 (0.073 – 0.325)	<0.001
10+ years	0.140 (0.048 – 0.410)	<0.001	0.268 (0.082 – 0.881)	0.030
CD4 at ART initiation				
Severe	1		1	
Advanced	0.654 (0.281 – 1.523)	0.325	0.512 (0.219 – 1.198)	0.123
Mild	0.107 (0.015 – 0.764)	0.026	0.057 (0.007 – 0.462)	0.007
IPT during follow-up				
No	1		1	
Yes	0.074 (0.023 – 0.236)	<0.001	0.161 (0.047 – 0.547)	0.003
ART during follow-up				
No	1		1	
Yes	0.179 (0.101 – 0.317)	<0.001	0.145 (0.078 – 0.270)	<0.001

Discussion

- We showed and independent and additive impact of IPT and ART on incident TB disease in HIV+ children, adding to previous evidence (Zar, *BMJ* 2006; Frigati, *Thorax* 2011)

- However the value of IPT for children on ART has been called into question of late (Schaaf, *SAMJ* 2013)

- Intensity of community transmission of TB and availability of contact investigation/management will impact the relative advantages of IPT being offered selectively versus broadly

Discussion

- In Vietnam (one of the top 22 high-TB burden countries), this study provided much-needed local data to convince local clinicians of the value and, more importantly, safety of IPT

- Clinician reluctance is much improved after dissemination of these findings in country

- LIMITATIONS:
  - Analyse data looking at timing of TB disease post-ART – help discriminate IRIS from new infection
  - Tolerability was assessed in a select population

Conclusions

- IPT was safe and effective for prevention of TB disease in children living with HIV in Vietnam.
- IPT discontinuation due to side effects occurred in only 1% of patients, and 95% completed the full course.
- ART let to a 76% reduction in active TB incidence, while those who received both ART and IPT had a 97% reduction. These results support the WHO recommendation for routine use of IPT in HIV+ children