

# Complications of BCG vaccination in HIV infected and uninfected children; evidence from the Children with HIV Early Antiretroviral Therapy (CHER) Study

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## INTRODUCTION

In HIV-infected infants, bacille Calmette-Guérin (BCG) may cause severe local, regional or distant/disseminated disease and in those starting ART, immune reconstitution inflammatory syndrome (IRIS). From retrospective studies, the risk for distant/disseminated BCG is 329-417/100 000 vaccinations (1) and BCG-IRIS 2.7% (2). There are no prospective studies quantifying BCG complications or management.

We evaluated a cohort of children from two parallel trials from the CIPRA-SA collaborative program. 415 HIV-positive infants were enrolled in the CHER trial and 250 HIV negative infants in CIPRA Project 4, which evaluated the immunogenicity of childhood vaccines in infected and uninfected infants.

Three groups of infants were compared: HIV-infected infants (according to CD4%); HIV uninfected infants born to HIV infected mothers and HIV uninfected infants of HIV negative mothers.

**Table 1: Treatment allocation for cohort**

Group	HIV-1 Status	N	CD4% at enrollment	Protocol ART allocation	On ART At analysis
1	Unexposed Uninfected	125	Not Applicable	Not Applicable	Not Applicable
2	Infected	125	≥25%	Delay until CD4 <20% (<25% from August 2006) or CDC Stage C or severe B	83
3	Infected	252	≥25%	Receive from 6-12 weeks	250
4	Infected	40	<25%	Receive from 6-12 weeks	40
5	Exposed Uninfected	125	Not Applicable	Not Applicable	Not Applicable

## METHODS

Infants were enrolled between 6 and 12 weeks of age. Local reactions to BCG were recorded at every visit. All infants received intradermal Danish strain BCG in the right deltoid area in the 1st week of life.

We present data after a median follow-up of 40 (IQR: 24-58) weeks when a Data Safety Monitoring Board recommended unblinding of the CHER study, enabling us to report on BCG-events.

Investigations and management of BCG events were not specified by the protocol.

### CASE DEFINITIONS OF BCG ENTITIES (3)

**Local:** Lesions at the injection site

**Regional:** Regional nodes and other contiguous lesions

**Distant:** Culture-proven involvement beyond the local or regional sites

**Disseminated:** Culture from >1 distant site OR blood / bone marrow

**BCG-associated IRIS:** Symptoms ≤6 months after initiation of HAART

New onset or exacerbation of local (injection site) abscess or ulcer AND/OR

New onset of regional adenitis ipsilateral to the vaccination site AND/OR

**Dual disease:** Any BCG entity with suspected or confirmed

*Mycobacterium tuberculosis* illness

*M. tuberculosis* complex can only be differentiated into *M. tuberculosis* or BCG through PCR or biochemical differentiation

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## RESULTS

**Table 2: Comparison of BCG reactivity measured by scar at 6 months in HIV-infected vs HIV-uninfected infants**

BCG Scar	HIV+	HIV-	P-value
No	3	1	
Yes	260	249	0.62

Odds Ratio 3.0 (0.1 - 74.9)

### BCG ADVERSE EVENTS

35/417 HIV-infected children enrolled had an adverse event to BCG

•2 had regional adenitis preceding HAART

•33 of 373 children initiating HAART developed regional IRIS

**Prevalence for IRIS : 8.8% (33/373)**

Incidence for IRIS :11.2 (7.7-15.8)/100 person years

### NON IRIS CASES (N=2)

Both had regional disease

•1 case also had local ulceration

•Dissemination was suspected but not proven in 1

Age of onset: 5.5 & 4.1 months respectively

Both had severe immune suppression - CD4 =340/32% & 243/17.6%

Both received anti-tuberculosis treatment

Adenitis resolved in both

### IRIS CASES (N=33)

All 33 cases had regional adenitis

7 (21%) where thought to have PTB during the time of IRIS

•1 Proven *M. tuberculosis* complex cultured from sputum

•6 Combination of clinical features, CXR and Tuberculin Skin Test

### Resolution of IRIS occurred in 31 / 33 infants

3 Deaths occurred

Case 1: (Early ART arm) regional adenitis after 5.5 months on ART, ART stopped due to hepatitis. Demised from gastroenteritis. Resolution of the adenitis had not been noted at the time of death.

Case 2: (Deferred arm). Defaulted and cause of death unknown. Presumed dual disease with *M. tuberculosis* complex cultured from sputum. Ongoing adenitis. Died after 9 months on ART and 6 months of TB treatment. Poor CD4 response to ART. An association with BCG could not be excluded:

Case 3: (Baseline CD4% <25% / Group 4) Infant demised 8 months after resolution of BCG IRIS.

**Table 3: CD4 count / percentage & Weight for Age Z-score (WAZ) at ART initiation in infants with & without BCG-IRIS**

	Cases with BCG-IRIS N = 33	Cases with no BCG-IRIS N = 340	P-value
<b>Median CD4 Count (IQR)</b>	875 (476 - 1765)	1838 (1242 - 2557)	<0.0001
<b>Median CD4 % (IQR)</b>	23.0% (15.8% - 36.8%)	31.5% (24.1% - 38.4%)	0.002
<b>Median WAZ (IQR)</b>	-1.5 (-2.5-0.5)	0.9 (-1.7- 0.0)	0.007

**Table 4: BCG-IRIS in infants with baseline CD4 ≥25% Early vs Deferred ART**

	Deferred Arm (n=83)	Early Treatment Arm (n=250)	P-value / Odds Ratio
Cases of IRIS(CI)	13/83: 15.7% (8.6% - 25.3%)	13/250: 5.20% (2.8% - 8.7%)	P=0.004 OR= 3.4 (1.5 - 7.7)
Incidence	27.9 Events per 100 person years	6.4 Events per 100 person years	

**Table 5: Clinical features of infants with BCG-IRIS: ART initiated CD4 <25% vs ≥25%**

	ART initiated with CD4% <25% N =19	ART initiated with CD4% ≥25% N =14	P-value
<b>Median Age (months) (IQR)</b>	4.3(3.3-5.4)	3.6 (3.4 - 5.1)	0.6
<b>Median WAZ (IQR)</b>	-1.5 (-2.7 - -0.7)	-1.0 (-1.6 - -0.2)	0.3
<b>Median Time from ART start to BCG IRIS (months) (IQR)</b>	0.9 (0.5 - 1.1)	1.3 (0.5 - 1.8)	0.5
<b>Median Time from start of BCG IRIS to resolution (months) (IQR)</b>	4.0 (3.4 - 8.0)	3.9 (3.3 - 6.4)	0.6
<b>Staging at time of IRIS : B or C</b>	7	4	
<b>N or A</b>	12	10	0.7

**Table 6: Time to resolution of regional IRIS in treated vs untreated subjects**

Any Anti-tuberculosis or Steroid Treatment	Yes	No	P-value
Median Time from start of BCG IRIS to resolution (months) (IQR)	3.9 (2.8 - 7.4)	4.5 (3.3 - 9.5)	0.5

## DISCUSSION

In May 2007, the WHO revised its guidance about BCG vaccination for children born to HIV-infected mothers and recommended that it should not be given to children known to be HIV infected. By that time, the CHER trial was fully recruited.

HIV-infected infants receiving BCG at birth have a high risk of BCG-associated IRIS.

Associated factors are lower CD4 count/percentage and low WAZ

In infants with baseline CD4 ≥25%, Early ART is associated with significantly less IRIS than deferred ART

Children in the deferred Arm developed IRIS sooner after ART initiation with longer time to resolution

Antituberculosis drugs +/- steroids did not improve the time to resolution.

There is no difference in BCG scar formation at 6 months between HIV infected and uninfected infants.

## CONCLUSIONS

Early ART is associated with a significant reduction in BCG-associated IRIS, probably by limiting the degree of CD4 depletion

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