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Early antiretroviral treatment reduces risk of bacille Calmette-Guérin immune reconstitution adenitis

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Abstract

Setting—Two centres in Soweto and Cape Town, South Africa.

Objective—To assess the effects of timing of initiation of antiretroviral treatment (ART) and other factors on the risk of bacille Calmette-Guérin (BCG) related regional adenitis due to immune reconstitution inflammatory syndrome (BCG-IRIS) in human immunodeficiency virus (HIV) infected infants.

Design—HIV-infected infants aged 6–12 weeks with CD4 count $\geq 25\%$ enrolled in the Children with HIV Early Antiretroviral Therapy (CHER) Trial received early (before 12 weeks) or deferred (after immunological or clinical progression) ART; infants with CD4 count $< 25\%$ all received early ART. All received BCG vaccination after birth. Reactogenicity to BCG was assessed prospectively during routine study follow-up.

Results—Of 369 infants, 32 (8.7%) developed BCG-IRIS within 6 months of starting ART, 28 (88%) within 2 months after ART initiation. Of the 32 cases, 30 (93.8%) had HIV-1 RNA $> 750\,000$ copies/ml at initiation. Incidence of BCG-IRIS was 10.9 and 54.3 per 100 person-years (py) among infants with CD4 count $\geq 25\%$ at enrolment receiving early (at median age 7.4 weeks) vs. deferred (23.2 weeks) ART, respectively (HR 0.24, 95% CI 0.11–0.53, $P < 0.001$). Infants with CD4 count $< 25\%$ receiving early ART had intermediate incidence (41.7/100 py). Low CD4 counts and high HIV-1 RNA at initiation were the strongest independent risk factors for BCG-IRIS.

Conclusions—Early ART initiation before immunological and/or clinical progression substantially reduces the risk of BCG-IRIS regional adenitis.

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Keywords

BCG; immune reconstitution inflammatory syndrome; paediatric HIV

BACILLE CALMETTE-GUÉRIN (BCG) protects immunocompetent children against miliary tuberculosis (TB) and TB meningitis, but there are safety and efficacy concerns in human immunodeficiency virus (HIV) infection.¹⁻⁴ The World Health Organization guidelines recommend avoiding BCG immunisation in HIV-infected infants due to the increased risk of dissemination.^{5,6} In South Africa, however, all neonates are still vaccinated, regardless of HIV exposure, as the prevalence of TB and HIV is high and HIV diagnosis before 6 weeks of age is not yet feasible.^{5,7-9}

BCG-related adverse events are classified as local, regional and distant or disseminated disease.^{10,11} TB and BCG disease may occur concurrently.^{11,12} Complications occurring soon after initiation of antiretroviral treatment (ART) are usually ascribed to immune reconstitution inflammatory syndrome (IRIS).^{11,13} BCG-related regional adenitis due to IRIS (BCG-IRIS) was described in respectively 6% and 15% of children in two South African cohorts.^{12,14} However, these and other reports only included children starting ART following immunological or clinical decline.^{11,12,14,15} Guidelines based on the Children with HIV Early Antiretroviral Therapy (CHER) Trial recommend ART for all HIV-infected infants aged <12 months.^{5,16} As immunosuppression is a risk factor for IRIS, early ART initiation in infants should lower the risk of BCG-IRIS; this, however, has not been evaluated.^{12,13}

We evaluated the effect of timing of ART initiation on the risk of BCG-IRIS among infants in the CHER trial. We also assessed other risk factors and described the clinical spectrum, management and outcome of cases.

Methods

Study population

In the main section of the CHER trial, Part A, HIV-infected infants aged 6–12 weeks with CD4 count $\geq 25\%$ were randomised to deferred or immediate ART in two South African centres (the Perinatal HIV Research Unit in Soweto and the Children's Infectious Disease Clinical Research Unit [KIDCRU] in Cape Town).¹⁶ In the deferred arm, ART was commenced when CD4% declined to below 25% or following the development of CDC Stage C or pre-defined severe Stage B disease. A small number of infants with CD4% < 25% at screening were recruited into Part B of the CHER trial and received immediate ART. All infants were given intradermal Danish SSI 1331 strain BCG in the right deltoid area during the first week of life. In June 2007, after a median follow-up of 40 weeks, the Data Safety Monitoring Board found that early treatment reduced mortality by 76%.¹⁶ All infants who started ART with subsequent follow-up by 20 June 2007 were included in the analysis, apart from those diagnosed with BCG-related regional adenitis before ART initiation in the deferred ART arm. Approval for the CHER study and for the publication of data from the study was obtained from the Institutional Review Boards at both sites.

Follow-up and case-definition

Infants had follow-up visits for clinical review and CD4 measurements every 3 months.¹⁶ HIV-1 RNA at ART initiation was measured using standard Roche Amplicor (Roche, Branchburg, NJ, USA) monitor assay version 1.5 RNA, with an upper limit of detection of 750000 copies/ml.

Reactogenicity to BCG vaccination was assessed prospectively. The case definition for BCG-adenitis IRIS (BCG-IRIS) was the development of ipsilateral axillary lymph node enlargement $\geq 10 \text{ mm} \times 10 \text{ mm}$ within 6 months of ART initiation, regardless of additional regional involvement and/or suppuration. Infants with BCG-IRIS and TB (either confirmed by isolation of *Mycobacterium tuberculosis* or presumptively diagnosed) occurring on overlapping time-frame were considered to have dual disease.^{11,17} A positive Mantoux test was defined as induration $\geq 5 \text{ mm}$. Speciation of *M. tuberculosis* was performed in Cape Town, but not in all cases from Soweto. Infants with suspected IRIS as well as dual disease were investigated and managed at the clinician's discretion. Information on clinical presentation, diagnosis, treatment and outcome of infants fulfilling the BCG-IRIS case definition were manually extracted from clinical records and merged with data from the main database.

Statistical analysis

To estimate the incidence of BCG-IRIS, follow-up for each infant was considered from the date of ART initiation until the earliest of the date of the diagnosis of BCG-IRIS, the date of the last clinic visit or 6 months after starting treatment. Time to diagnosis of BCG-IRIS was estimated for each ART group using Kaplan-Meier methods. The effect of starting ART early compared to deferral until immunological or clinical progression on risk of BCG-IRIS was assessed based on infants in Part A of the study only, using Cox proportional hazards regression and without adjusting for other factors at ART initiation. Parts A and B were then combined to assess the effects of the following factors at initiation: age, sex, CD4% and absolute count, HIV-1 RNA viral load, and weight-for-age z-score (based on US standards for non-infected children).¹⁸ The ART group was not adjusted for in multivariable analyses. The individual effects of CD4% and count were estimated adjusting for other confounding factors, but not for each other. The effect of age was adjusted for CD4 count z-score rather than CD4% or absolute count, both of which decline with age.¹⁹ To allow for the possibility that CD4 and HIV-1 RNA levels are intrinsically different between HIV-infected male and female infants, the effect of sex was estimated with and without adjusting for CD4 and HIV-1 RNA levels at initiation.^{20,21} HIV-1 RNA values were categorised as $<$ or $>$ 750000 copies/ml in regression models, as 62% of children initiated ART at levels above the upper detection limit of the assay. Other covariates were analysed as continuous variables where appropriate, to increase power. Age was log-transformed to improve model fit. Non-linearity effects were assessed using a cubic spline term with knots at the 10th, 50th and 90th percentiles.²²

Among infants with BCG-IRIS, the median time to resolution from diagnosis was estimated for the following treatment strategies, allowing for censored data:²³ 1) medical intervention with anti-mycobacterial treatment specifically aimed for BCG (combinations including ofloxacin or/and ethambutol) and/or steroids; 2) incision and drainage without medical intervention; and 3) no medical or surgical intervention. All analyses were undertaken using STATA (version 10.0, STATA Corporation, College Station, TX, USA).

Results

Analyses were based on 369 infants initiating ART (Table 1): 250 infants in Part A (early ART A, CD4% $\geq 25\%$ at enrolment) and 40 in Part B (early ART B, CD4% $< 25\%$) received early ART, and 79 infants received deferred ART in Part A (deferred ART, CD4% $\geq 25\%$). Of the 125 infants randomised to deferred ART, 46 were excluded: two developed BCG regional adenitis before initiating ART, 41 had not started ART (15 due to death and two lost to follow-up), and three initiated ART without subsequent follow-up by 20 June 2007. BCG-related complications were not noted as either the cause of death or contributing to death in any of the 15 infants who died prior to initiating treatment.¹⁶ Infants on early

ART initiated ART at a median age of 7.4 weeks (interquartile range [IQR] 6.5–8.8) in Part A and 9.3 weeks (IQR 8.1–10.5) in Part B. In the deferred ART group, median age at initiation was 23.2 weeks (17.4–33.6), with nine (11%) <12 weeks of age. CD4% at ART initiation was similar in the deferred ART and early ART B groups (Table 1). Fifty-five per cent of infants in the early ART A group had HIV-1 RNA level >750000 copies/ml, compared to respectively 80% and 78% in the deferred ART and early ART B groups.

Of the 369 infants, 32 (8.7%) were diagnosed with BCG-related regional adenitis within 6 months of ART initiation: 13 (16%) in the deferred ART group, 12 (5%) in the early ART A group and seven (18%) in the early ART B group. Most cases (88%) occurred within 2 months of ART initiation, with only one after 3 months. All but two of the 32 cases had HIV-1 RNA level > 750 000 copies/ml at initiation.

The overall incidence of BCG-IRIS was 21.2 per 100 person-years (py). In Part A, the rate was 10.9 per 100 py (95% confidence interval [CI] 6.2–19.1) in the early ART group compared to 54.3 (31.5–93.4) per 100 py in the deferred ART group (hazard ratio [HR] 0.24, 95% CI 0.11–0.53, $P < 0.001$). The early ART group from Part B experienced only a slightly lower rate (41.7/100 py, 95% CI 19.9–87.6) than the deferred ART group. Kaplan-Meier curves of time to BCG-IRIS are shown in the Figure.

In multivariable analyses, low CD4 count (HR 0.89 per 100 cells/mm³, 95% CI 0.84–0.94, $P < 0.001$) and HIV-1 RNA > 750 000 copies/ml (HR 5.80, 95% CI 1.37–24.54, $P = 0.017$) were the strongest predictors of BCG-IRIS (Table 2). After adjusting for CD4 z-score and HIV-1 RNA, age appeared to show a non-linear effect (P value of cubic spline term = 0.015), with the risk of BCG-IRIS increasing with age until 12 weeks, but then decreasing from around 24 weeks (Table 2). Weak evidence for this initial increase in risk with age remained when including infants in the randomised early ART A group only (HR 1.28 per week, 95% CI 0.95–1.73, $P = 0.110$). After adjusting for age and HIV-1 RNA, low CD4% had only a weak effect (HR 0.81 per 5%, 95% CI 0.65–1.01, $P = 0.058$). Females had a lower risk of BCG-IRIS after adjusting for age only (HR 0.40, 95% CI 0.19–0.84, $P = 0.015$), although the sex difference was less apparent when further adjusted for CD4 count and HIV-1 RNA (HR 0.56, 95% CI 0.25–1.18, $P = 0.129$). There was no association with weight-for-age z-score after accounting for age and immunological and virological status.

Clinical signs and symptoms

The lymph nodes progressed to suppuration in 17 (53%) of the 32 cases, with fistulae occurring in 14 (44%). Eight (25%) had concurrent BCG and TB disease; two initiated ART while on TB treatment and six were diagnosed with TB within 6 months after ART initiation and prior to resolution of BCG adenitis. In five cases the diagnosis of TB was based on history of contact, symptoms suggestive of TB and radiographic features. In one case, *M. tuberculosis* complex was cultured from a site other than a regional arm lymph node. Fine needle aspiration of a regional axillary lymph node was performed in 28 (88%) infants. Organisms were isolated in 25 cases, of which 16 (64%) grew *M. tuberculosis* complex, with BCG confirmed in six. No other pathogens were identified. The clinical features nevertheless supported BCG adenitis IRIS in the remainder. Of 17 cases with BCG IRIS but without TB, 14 (82%) had reactive skin tests, with eight having an induration ≥ 10 mm.

Treatment and outcome

Treatment of adenitis varied widely (Table 3). At last follow-up, adenitis had resolved in 29 of 32 cases, including all of the 10 infants who received no medical or surgical intervention. Two of the remaining three infants died before resolution, one of diarrhoeal disease and the other, with dual BCG and TB disease, after relocating to another province. This child had

culture-confirmed *M. tuberculosis* complex disease that was not further speciated. Median time to resolution was 4.0 months (IQR 3.2–7.5), and was similar across the treatment strategies.

Discussion

We evaluated the incidence of BCG-related regional adenitis IRIS in HIV-infected infants followed from early in life and starting ART at different ages and CD4 values. We found that starting early ART prior to CD4 depletion or clinical progression at a median age of 7 weeks resulted in a 4-fold reduction in risk of BCG-IRIS compared to deferring ART.

Low CD4 count and high HIV-1 RNA viral load at ART initiation were the strongest risk factors for BCG-IRIS. However, CD4% had only a weak effect after adjusting for age and viral load, possibly because the majority of infants initiated ART early and at high CD4% (71% had CD4% \geq 25%). The higher prognostic value of absolute CD4 count compared to percentage is consistent with an analysis of untreated children in the United States and Europe, where CD4 count was more predictive of progression to acquired immune deficiency syndrome or death, even in infancy.²⁴ HIV-1 RNA level at ART initiation was >750000 copies/ml in 30 (94%) of the 32 infants who developed BCG-IRIS, compared to only 60% of those who did not. The role of elevated viral load in the development of BCG-IRIS could be mediated through increased immune activation. Viral load was also shown to be an independent risk factor by Nuttall et al.¹⁴ However, in another South African cohort in which IRIS events were combined (BCG-related and other conditions), no evidence of this association was observed.¹²

Age at ART initiation was independently associated with risk of BCG-IRIS, although the relationship was non-linear (P for nonlinearity 0.015); risk of IRIS increased with age until around 12 weeks, with some decrease later in infancy. There remained weak evidence of this early increase in risk when the analysis was restricted to infants randomised to early ART. This age trend has not been reported before and could potentially be due to the increase in BCG organism load in the immediate weeks after vaccination. As the subsequent decreased risk of BCG-IRIS in older infants at ART initiation was based on sparser data, this could have been due to chance. It could also be partly explained by a 'survivor bias' effect, as all infants starting treatment from the age of 12 weeks onwards were from the deferred ART arm only; those initiating at older ages would likely be those with better HIV prognosis and thus a lower risk of BCG-IRIS, as the more severely affected infants will have reached the criteria for starting ART or died earlier in infancy. A lower risk of IRIS at older age at ART initiation was also reported previously.^{12,14} These studies of older children could also have been affected by survivor bias, as ART initiation depended on immunological and clinical criteria. Finally, although we attempted to estimate the effect of age adjusting for viral load (analysed as $<$ or $>$ 750000 copies/ml), 'residual' confounding may have occurred, contributing to the observed trends with age at initiation among both the younger and older infants; HIV-1 RNA viral load increases sharply with age during the first weeks of life, peaking at around 3 months.²¹

In our study, we adopted a clinical case definition for BCG-IRIS; HIV-1 RNA viral load was not available at the time of diagnosis. Given the early onset of symptoms and the cost of the viral load and CD4 assays, robust clinical case definitions are appropriate in lower-resource settings. Although local disease was severe, we did not observe any cases of proven distant or disseminated BCG, possibly because the CHER trial children were intensively monitored so that disseminated disease did not have time to develop; the exception was the child who defaulted from follow-up and who subsequently died. The study did not mandate fine-needle aspiration for diagnostic purposes, as right axillary adenitis after ART initiation

was considered to be characteristic of BCG-IRIS. BCG-IRIS is more common than TB IRIS in HIV-infected South African infants.¹² We found a relatively high proportion (25%) of BCG-IRIS cases with concurrent TB disease. Six of the eight dual cases developed TB within 6 months of ART. The overlapping clinical time period and robust Mantoux skin test response observed in these infants on ART complicates the diagnosis of TB.

Interferon-gamma release assays were undertaken in some infants but were too few to permit interpretation; negative results do not exclude TB.²⁵

Clinical trial data to guide appropriate therapy for BCG disease in HIV-infected children are lacking.¹³ Although no conclusions about the efficacy of different approaches can be drawn due to potential selection bias and the small number of cases, we observed minimal difference in time to resolution of adenitis between treatment strategies. Nearly a third of the cases resolved spontaneously, suggesting that regional disease may sometimes only require monitoring and symptomatic relief, consistent with anecdotal evidence.^{13,26} The value of anti-mycobacterial treatment for regional adenitis remains unclear, with potential drug-drug interactions with antiretroviral drugs and risk of compromising adherence complicating decision making.^{13,14} Danish strain BCG is resistant to low-dose isoniazid, pyrazinamide and ethionamide.²⁷

Conclusion

Early initiation of ART before immunological and clinical progression reduces the risk of BCG-IRIS substantially among HIV-infected infants vaccinated with BCG at birth. Standardised treatment protocols for BCG adenitis based on evidence from clinical trials are required.

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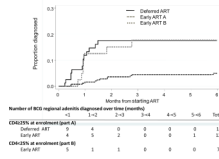


Figure 1. Kaplan-Meier curves of time from starting ART to diagnosis of BCG-related regional adenitis, by ART groups.

Table 1

Children included in analysis: characteristics at ART initiation and subsequent diagnosis of BCG-related regional adenitis due to IRIS

	Deferred ART Group ¹ (CD4≥25% at enrolment)	Early ART Part A Group (CD4≥25% at enrolment)	Early ART Part B Group (CD4<25% at enrolment)	Overall
Number of children	79 ²	250	40	369
Female (%)	45 (57%)	145 (58%)	19 (48%)	209 (57%)
Characteristics at ART initiation				
Age (weeks)				
Median (IQR)	23.2 (17.4 to 33.6)	7.4 (6.5 to 8.8)	9.3 (8.1 to 10.5)	8.3 (7.0 to 11.0)
Range	8.0 to 71.8 ³	5.7 to 12.0	6.1 to 12.0	5.7 to 71.7
<12 weeks (%)	9 (11%)	250 (100%)	40 (100%)	299 (81%)
Median (IQR) CD4%	21% (17 to 28%)	35% (29 to 41%)	20% (17 to 24%)	31% (23 to 38%)
CD4% < 25% (%)	53 (68%)	19 (8%) ⁴	29 (78%) ⁴	101 (29%)
Median (IQR) CD4 count (cells/mm ³)	1039 (662 to 1528)	2002 (1493 to 2745)	1433 (653 to 2204)	1779 (1136–2496)
Median (IQR) CD4 count z-score	-1.2 (-1.7 to -0.7)	-0.2 (-0.7 to 0.5)	-0.7 (-1.7 to 0.0)	-1.0 (-1.8 to -0.3)
Median (IQR) weight-for-age z-score	-1.1 (-2.1 to 0.0)	-0.8 (-1.5 to 0.0)	-1.1 (-2.2 to 0.0)	-0.9 (-1.7 to 0.0)
HIV-1 RNA > 750,000 copies/ml (%)	53 (80%)	138 (55%)	31 (78%)	222 (62%)
BCG regional adenitis diagnosed within 6 months after ART initiation				
Number of cases (%)	13 (16%)	12 (5%)	7 (18%)	32 (8%)
Rate per 100 person-years (95% CI)	54.3 (31.5 to 93.4)	10.9 (6.2 to 19.1)	41.7 (19.9 to 87.6)	21.2
Estimated probability of developing BCG-IRIS ⁵ (95% CI)	17.6% (10.6 to 28.3%)	5.0% (2.9 to 8.8%)	17.5% (8.8 to 33.2%)	9.1%

¹ ART deferred until child fulfilled clinical or immunological criteria.

² Excluded 2 children who developed BCG-related regional adenitis prior to ART initiation

³ 6 children in the deferred ART group were older than 1 year at initiation.

⁴ Infants in the Early ART groups may have CD4 measured following enrolment prior to starting ART; CD4% had dropped to <25% for some in part A and increased to ≥25% for some in part B.

⁵ Estimated using Kaplan-Meier methods.

Table 2
Associations between factors at ART initiation and BCG-related regional adenitis due to IRIS

Factors	Rate per 100 person-years (number of cases/PY)	Univariable analyses		Multivariable analyses	
		Hazard Ratio ¹ (95% CI)	P-value	Hazard Ratio ¹ (95% CI)	P-value
Gender					
Male	33.5 (21/62.8)	1	0.010	1	
Female	12.4 (11/88.8)	0.38 (0.19–0.80)		0.56 (0.26–1.18) ³	0.129
Age (weeks)					
< 8	8.0 (6/75.1)	1	<0.001	1	0.029
8 to 11	23.2 (13/56.1)	4.92 (2.20–11.01)		2.56 (1.17–5.64)	
12 to 23	99.8 (10/10.0)	9.16 (3.05–27.56)		2.46 (0.79–7.61)	
≥ 24	29.0 (3/10.3)	4.90 (1.51–15.90) ²		1.07 (0.26–4.40) ²	
CD4%					
< 20%	60.8 (12/19.7)	0.68 (0.55–0.83) per 5%	<0.001	0.81 (0.65–1.01) per 5%	0.058
20 to 24%	40.7 (7/17.2)				
25 to 29%	11.2 (3/26.9)				
≥ 30%	11.3 (9/79.4)				
CD4 count cells/mm ³					
< 1000	72.1 (17/23.6)	0.86 (0.81–0.91) per 100 cells/mm ³	<0.001	0.89 (0.84–0.94) per 100 cells/mm ³	<0.001
1000 to 1999	19.1 (11/57.6)				
≥ 2000	4.8 (3/62.1)				
HIV-1 RNA (copies/ml)					
< 750,000	3.4 (2/59.1)	1		1	
> 750,000	33.7 (30/88.9)	9.49 (2.27–39.70)	0.002	5.80 (1.37–24.54)	0.017
Weight-for-age z-score					
< -2	57.6 (11/19.1)	0.67 (0.49–0.91) per unit	0.010	0.80 (0.60–1.08) per unit	0.144
-2 to < -1	17.2 (8/46.6)				
-1 to < 0	18.2 (8/43.9)				
≥ 0	10.5 (4/38.0)				

¹In Cox regression models, age, CD4%, CD4 count and weight-for-age z-score were analysed as continuous variables while HIV-1 RNA was defined as < or > 750,000 copies/ml.

² Age was log transformed and fitted with a cubic spline (p-value for cubic term=0.015). To present the estimated effect of age, we derived from the fitted model the hazard at the approximate median age value within each of the age groups defined (age 7 weeks for the group <8 weeks, 9.5 for 8–11 weeks, 20 for 12–23 weeks and 36 for ≥ 24 weeks), and then calculated the corresponding hazard ratios.

³ The estimated hazard ratio for females compared to males was 0.40 (95% CI 0.19–0.84; p=0.015) when adjusted for age only (to allow for the possibility that the effect of gender is mediated through CD4 and HIV-1 RNA), and 0.56 (0.26–1.18; p=0.129) when CD4 count and HIV-1 RNA were further adjusted for.

Table 3

Management of children with BCG-related regional adenitis due to IRIS

Management	Number of children (%)	BCG adenitis resolved by last follow-up	Median (IQR) number of months to resolution from diagnosis
No medical or surgical intervention	10 (31%)	10	3.9 (3.2–9.5)
Anti-mycobacterial therapy and/or steroids	15 ¹ (47%)	13	3.8 (2.2–6.8)
Incision and drainage only	7 (22%)	6	4.0 (2.3–4.6)
Overall	32 (100%)	29 ²	4.0 (3.2–7.5)

¹ Four children were treated with anti-mycobacterial therapy, 9 with steroids and 2 with both anti-mycobacterial therapy and steroids. Incision and drainage was performed in 8 of the 15 children.

² BCG adenitis had not resolved by last follow-up in one child and two died before resolution.