Bacillus Calmette–Guérin (BCG) vaccine-induced complications in children treated with highly active antiretroviral therapy

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KEYWORDS
Bacillus Calmette–Guérin; HIV-1; Highly active antiretroviral therapy; Adverse events

Summary
Objective: To describe the frequency, risk factors, and clinical features of bacillus Calmette-Guérin (BCG) complications in HIV-infected children treated with highly active antiretroviral therapy (HAART).

Methods: A retrospective study of children started on HAART between August 2002 and November 2004 was completed.

Results: Six percent (21/352; 95% CI 3.7–8.0%) developed BCG complications. All developed ipsilateral axillary lymphadenitis; one child had suspected disseminated BCG infection. There were 14 females; median age at start of HAART was 5 months. BCG disease developed a median of 34 days after starting HAART. At baseline and 6 months into HAART, the median CD4 percentage and log10 viral load were 12.3/6.1 and 23.9/4.5, respectively. Seventeen (81%) of the patients were treated with either zidovudine or stavudine combined with lamivudine and ritonavir. Young age and high baseline viral load were independent risk factors for development of BCG complications. Mycobacterium bovis BCG was isolated in 70% of patients who underwent incision and drainage of abscesses at the vaccination site or regional lymph nodes.

Conclusions: This study identified a high prevalence of BCG complications in children on HAART. A clinical case definition of BCG immune reconstitution syndrome independent of laboratory parameters for use in resource-limited settings should be developed.

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Introduction

South Africa has one of the largest pediatric HIV epidemics. In mid-2006 the Medical Research Council of South Africa estimated that there were approximately 300 000 HIV-infected children under 15 years of age living in the country.1 An increasing number of infected children have been commenced on highly active antiretroviral therapy (HAART); by mid-2006 more than 21 000 children were on HAART.2

The bacillus Calmette–Guérin (BCG) vaccine contains a live attenuated strain of Mycobacterium bovis. South Africa has administered routine neonatal BCG vaccination since 1974. Between July and December 2000, the route of administration was changed from percutaneous to intradermal. At the same time, the BCG strain was changed from Tokyo 172 to Danish 1331 (Statens Institut, Copenhagen, Denmark).3 The World Health Organization (WHO) recommends that HIV-infected children should not receive BCG vaccination.4 In practice, HIV DNA PCR testing is rarely performed during the first few weeks of life and virtually all newborns, irrespective of their HIV status, receive BCG vaccination in South Africa.

The spectrum of adverse events after BCG vaccination includes persistent ulceration and discharge from the vaccination site, regional lymphadenitis with or without suppuration and/or fistulation, and disseminated BCG infection.5,6 Transition to intradermal administration in South Africa was associated with a transient increase in the frequency of adverse events, most likely related to the technique of administration.7 Publications have recently started describing the spectrum of BCG adverse events in the setting of HIV infection.8–14 BCG vaccination significantly increases the risk for disseminated infection.9,10 Vaccination site abscess formation and/or regional supplicative adenitis after the commencement of HAART have been documented in several reports.8,11–14 In this study, we describe the prevalence of and risk factors for BCG complications in HIV-infected children after starting HAART.

Methods

Patients

Between August 1 and November 30, 2004, 352 children were enrolled in a public sector antiretroviral treatment program at the Red Cross Children’s Hospital in Cape Town, South Africa. The indications for starting HAART concurred with existing WHO recommendations for resource-limited settings.15 At enrolment, clinical and laboratory evaluation included CD4+ lymphocyte count and percentage and HIV-1 RNA PCR (viral load) measurement. All children commencing HAART attend our clinic prior to starting treatment, two weeks after starting treatment, monthly for 6 months, and 1–3 monthly thereafter to monitor clinical progress and to identify adverse events. The monitoring plan included 6-monthly CD4 count and percentage, and viral load.

Regional BCG disease was defined as persistent ulceration, abscess or fistula limited to the BCG vaccination site (intradermal injection into skin overlying right deltoid muscle), or enlarged or suppurative lymphadenopathy of the right axilla. Progressive regional disease was defined as enlarged or supplicative lymphadenopathy with or without fistula formation, extending beyond the right axilla (e.g., to the ipsilateral supravacular or cervical lymph nodes). Suspected disseminated BCG disease was defined as identification of M. bovis BCG from suppurrative regional lymphadenitis and gastric lavage samples in the same patient with a compatible clinical syndrome.6,16 However, not all patients who underwent percutaneous aspiration or surgical drainage of abscesses had gastric lavage specimens sent for mycobacterial culture. Mycobacterial blood or bone marrow cultures were not routinely performed. A multiplex PCR method was used to differentiate M. bovis BCG and other members of the M. tuberculosis complex following culture of pus obtained from suppurrative lymphadenitis or abscesses.17

Data collected and analyzed included: patient demographics, baseline CD4+ lymphocyte count and percentage measured by the PanLeucocating method,18 viral load measured by commercial assay (Nuclisens; bioMérieux, Boxtel, the Netherlands), date of starting HAART, HAART regimen, date that the BCG complication was first recorded by the attending doctor; nature of the BCG complication, management including surgical drainage of abscesses, and antimycobacterial chemotherapy. Limitation of resources prevented routine CD4 and viral load measurement at the time that the BCG complications presented. Weight-for-age Z-score (WAZ) was calculated using Epilinfo 2000, version 1.0 (Division of Surveillance and Epidemiology, CDC, Atlanta, GA, USA). Cutaneous delayed-type hypersensitivity (DTH) response to mycobacterial antigens (tuberculin skin testing) was not routinely performed prior to starting HAART or at the time that the BCG complications presented. Photographs of some of the lesions were taken with the consent of parents or legal guardians of children. Ethics approval was obtained from the Research Ethics Committee of the University of Cape Town to analyze aspects of the antiretroviral treatment program at the Red Cross Children’s Hospital, Cape Town (reference number: 261/2002).

Statistical analysis

Data were analyzed with STATA version 8.0 (Stata Corp., College Station, TX, USA). The 95% confidence interval (CI) for a binomial proportion was used to estimate the frequency of BCG complications. Baseline characteristics of children who did and did not develop BCG adverse events were compared using the two-sample Wilcoxon rank sum (Mann–Whitney) test for non-parametric continuous variables and the Chi-square or Fisher’s exact tests for categorical data. Multiple logistic regression analysis using a stepwise backward elimination procedure was performed to find the best predictive model for developing a BCG reaction. Comparison of baseline and 6-month characteristics of children who developed BCG reactions and in whom results at both time points were available were done using paired t-test or Wilcoxon rank sign test for normally and non-normally distributed data, respectively.

Results

Twenty-one out of a total of 352 (6%; 95% CI 3.7–8.0%) children starting HAART during the study period developed BCG complications. There were 14 females and seven males,
and the median age (interquartile range) at start of HAART was 5 months (3.8–8.5 months). Prior to commencing HAART, the median CD4+ lymphocyte count (×10⁹/l) (IQR) was 0.42 cells (0.17–0.86), the median CD4+ lymphocyte percentage (IQR) was 12.3 (8.8–16.3), and the HIV-1 log₁₀ viral load (IQR) was 6.1 (5.8–6.7). In 17 of the 21 patients (81%) the first-line HAART regimen comprised either zidovudine or stavudine combined with lamivudine and ritonavir. Other antiretroviral regimens included stavudine, lamivudine, and efavirenz (2); stavudine, lamivudine, and nevirapine (1); zidovudine, lamivudine, and lopinavir–ritonavir (1).

**Baseline risk factors for developing BCG complications**

Baseline clinical, immunological, and virological data are shown in Table 1. The baseline CD4+ lymphocyte count, CD4+ percentage, and viral load were available for 345 (98%), 338 (96%), and 311 (88%) children, respectively.

Children who developed BCG complications were younger at the start of HAART (p < 0.001) and had a higher HIV-1 log₁₀ viral load (p < 0.001) than those who did not. There was no significant difference in CD4+ lymphocyte count or percentage. There was a non-significant trend towards a greater number of BCG adverse events in female patients (p = 0.155).

BCG complications were more frequent in children whose HAART regimen included a protease inhibitor (PI) (p = 0.001). However, younger children were far more likely to be treated with a PI-containing regimen (p < 0.001) due to the lack of availability of non-nucleoside reverse transcriptase inhibitors in suitable formulations, and the desire to avoid using nevirapine in those children exposed to perinatal nevirapine. The apparent association with a PI-containing regimen disappeared once the effect of age had been controlled.

Since the majority (17/21; 81%) of BCG complications occurred in children aged 9 months or younger, a separate analysis was performed on this subset. Within this group of children, BCG complications occurred more frequently in female infants (p = 0.036), and there was a trend towards lower baseline CD4+ lymphocyte counts (p = 0.104).

In all the children (N = 352), the best predictive model for developing BCG complications included age and log₁₀ viral load (Table 2). Younger children were significantly more at risk with a 5.1% (95% CI 0.90—0.99) reduction in risk for each additional month of age. The adjusted odds ratio (OR) for every 1-unit increase in baseline log₁₀ viral load was 2.93 (95% CI 1.15—7.49). Gender was included in the model because of the trend towards a greater incidence of BCG adverse events among female patients, although this did not achieve significance (OR 2.66, 95% CI 0.91—7.82).

A separate multivariate model was determined for children aged 9 months and younger. There was no effect of age within this group; however higher viral load was an important predictor of developing complications (OR 3.29, 95% CI 1.01—10.79). This was not apparent in the univariate analysis. There was a non-significant trend towards a reduced likelihood of developing BCG complications in children with a higher baseline CD4+ lymphocyte count (OR 0.21, 95% CI 0.04—1.28 for every additional 1 × 10⁶ cells/l). There were also more BCG adverse events in females (OR 3.65, 95% CI 0.92—14.49).

**Response to HAART in children with BCG complications**

The CD4+ lymphocyte percent and count, log₁₀ viral load, and WAZ after 6 months of HAART were analyzed in 17 (81%), 16 (76%), and 19 (90%) of the children experiencing BCG complications, respectively (Table 3). The median gain (IQR) in CD4+ lymphocyte count was 0.60 × 10⁹/l (0.25—0.98) and percentage was 8.09 (2.82—12.85). The median reduction (IQR) in log₁₀ viral load was 2.17 (3.60—1.97). In two children the CD4+ percentage decreased (by 5.25 percentage points in one and by 2.07 percentage points in the other) and in one child the CD4+ lymphocyte count decreased by 73 × 10⁹ cells/l after 6 months on HAART. In two children the viral load increased after 6 months on HAART. In three children, baseline or 6-month laboratory tests were not performed and a further two children were lost to follow-up after developing BCG complications.

**Clinical features of BCG complications**

The 21 children presented to hospital with BCG complications a median (IQR) of 34 (15—60) days after starting HAART. All 21

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**Table 1** Baseline demographic data (univariate analysis)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No BCG complication (N = 331)</th>
<th>BCG complication (N = 21)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>179 (96.2%)</td>
<td>7 (3.8%)</td>
<td>0.065</td>
</tr>
<tr>
<td>Female</td>
<td>152 (91.6%)</td>
<td>14 (8.4%)</td>
<td></td>
</tr>
<tr>
<td>Age (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27 (9–55) (N = 330)</td>
<td>27 (9–55) (N = 330)</td>
<td>5 (3.8–8.5) (N = 21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD4+ cells (%)</td>
<td>12.0 (7–18) (N = 318)</td>
<td>12.3 (8.8–16.3) (N = 20)</td>
<td>0.55</td>
</tr>
<tr>
<td>CD4+ cell count (× 10⁹/l)</td>
<td>0.46 (0.21–0.85) (N = 325)</td>
<td>0.42 (0.17–0.86) (N = 20)</td>
<td>0.76</td>
</tr>
<tr>
<td>Log viral load</td>
<td>5.6 (5.1–6.1) (N = 293)</td>
<td>6.1 (5.8–6.7) (N = 18)</td>
<td>0.001</td>
</tr>
<tr>
<td>PI-containing regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>173 (98.3%)</td>
<td>3 (1.7%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>158 (89.8%)</td>
<td>18 (10.2%)</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as n (%) or median (interquartile range).
BCG, bacillus Calmette–Gue´rin; PI, protease inhibitor.

a Number of patients for whom data were available.
children had abnormally enlarged right axillary lymph nodes with or without suppuration (regional disease). Three (14%) children first presented to hospital following spontaneous discharge of pus from right axillary abscesses. Five children had new ulceration or abscess formation at the BCG vaccination site (right deltoid). In addition to right axillary abscesses, two (10%) children developed abscesses in the ipsilateral supraclavicular and lower cervical regions (progressive regional disease) (Figure 1).

Mycobacterial culture of material obtained from abscesses at the vaccination site, supplicative regional lymph nodes, or gastric lavage specimens, was performed in 10 of the 21 (48%) patients. Seven (70%) of these 10 cases had positive cultures for M. bovis with further identification of M. bovis BCG by PCR; in two cases the mycobacterial culture was contaminated by bacterial overgrowth, and in one case the mycobacterial culture was negative. Sensitivity testing was performed on three of the seven M. bovis BCG isolates and all three were sensitive to rifampin and isoniazid.

One of the 21 children had previously experienced persistent vaccine site ulceration and right axillary lymphadenitis following BCG vaccination prior to initiation of HAART. After starting HAART, this patient presented with spontaneous rupture of an abscess in the right axilla.

In one patient with failure to thrive and hepatosplenomegaly, M. bovis BCG was isolated from pus aspirated from a right axillary abscess as well as from two gastric lavage samples collected on different days during a hospital admission with fever and suspected septicemia. This patient was suspected of having disseminated BCG disease. However, the diagnosis was not confirmed by the culture of the organism from blood or deep tissue biopsies.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.95 (0.90—0.99)</td>
</tr>
<tr>
<td>Log viral load</td>
<td>2.93 (1.15—7.49)</td>
</tr>
<tr>
<td>Female gender</td>
<td>2.66 (0.91—7.82)</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval.

Table 2 Baseline demographic data (multivariate analysis)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>6 months</th>
<th>Change</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4+ cells (%)</td>
<td>12.32 (8.81—16.3)</td>
<td>23.35 (14.85—28.47)</td>
<td>11.03</td>
<td>0.0086</td>
</tr>
<tr>
<td>CD4+ cell count (&lt;10⁹/l)</td>
<td>0.42 (0.17—0.86)</td>
<td>0.58 (0.25—0.98)</td>
<td>0.16</td>
<td>0.0008</td>
</tr>
<tr>
<td>Log viral load</td>
<td>6.11 (5.38—6.7)</td>
<td>4.46 (2.60—5.44)</td>
<td>-1.65</td>
<td>0.0008</td>
</tr>
<tr>
<td>WAZ/SD</td>
<td>2.63 ± 0.90 (N = 21)</td>
<td>1.33 ± 0.33 (N = 19)</td>
<td>-1.30</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Data are expressed as median (interquartile range) or mean ± standard deviation.

BCG, bacillus Calmette–Gue´rin; WAZ, weight-for-age Z-score.

Table 3 Baseline and 6-month demographic data in children with BCG complications

Figure 1 BCG vaccine-induced complication presenting 34 days after starting HAART: ulceration at BCG vaccination site (right deltoid) and abscess formation at right axillary lymph nodes and supraclavicular region.
Management of BCG complications

Treatment of BCG complications was not standardized. Nine (43%) children underwent aspiration or formal incision and drainage of suppurative regional lymphadenitis. Six of these nine children also received anti-mycobacterial chemotherapy. Four children were treated with anti-mycobacterial chemotherapy and no surgical intervention. In eight (38%) children there was no surgical or medical intervention and the inflammatory swellings were closely monitored at regular intervals (Table 4). Anti-mycobacterial chemotherapy included a combination of rifampin, isoniazid, and ethionamide (n = 10); one child developed elevated liver enzymes and treatment was changed to a combination of isoniazid, ethionamide, and ofloxacin. One child was already receiving treatment for pulmonary tuberculosis with rifampin, isoniazid, and pyrazinamide for 3 months at the time that he developed the BCG complication, and this treatment was continued. There were no deaths attributable to BCG disease.

Discussion

The present study suggests that approximately 6% of HIV-infected children who receive intradermal BCG vaccination at birth may develop clinically significant BCG complications after starting HAART. The narrow 95% CI of 3.7–8.0% for a sample size of 352 children indicates that this is likely to be a relatively accurate estimate. A previous study reported that 3.1% of nearly 10,000 children examined, developed adverse events following BCG vaccination with the Danish 1331 BCG vaccine during the first few months of life. In that study the HIV status of the children was not established. Transition from percutaneous to intradermal route of administration may have been in part responsible for the relatively high prevalence of BCG complications in that study. Most of the affected children developed injection-site abscesses (41.0%), site oozing (36.3%), or lymphadenopathy (18%). In the present study, none of the BCG complications were limited to the vaccination site. All 21 children developed significant axillary lymphadenitis, three (14%) children presented with spontaneous rupture of axillary abscesses, two developed progressive regional disease with abscesses in the supraclavicular and cervical lymph nodes (Figure 1), and one had presumed disseminated BCG disease, suggesting that BCG complications in HIV-infected children are generally more severe. This deduction is supported by previous studies documenting high rates of disseminated BCG disease among HIV-infected children.9,10

In the face of mounting evidence of increased risk of serious BCG complications in HIV-infected children and the absence of studies evaluating the protective benefit of BCG in HIV-infected children, in May 2007 the Global Advisory Committee on Vaccine Safety (GACVS) advised the WHO that the benefits of potentially preventing severe tuberculosis are outweighed by the risks associated with the use of BCG vaccine. Children who are known to be HIV-infected, even if asymptomatic, should no longer be immunized with BCG vaccine. Where HIV testing is possible, BCG immunization should be deferred until the HIV status of the infant has been established, and should only be administered to HIV-uninfected infants.4

The temporal relationship between introducing HAART and the onset of BCG complications suggests that most of these adverse events are manifestations of the immune reconstitution inflammatory syndrome (IRIS). BCG complications presented a median of 34 days after starting HAART, and all except one child presented within 90 days after starting HAART. IRIS due to pathogens or opportunistic organisms is believed to be a consequence of the restoration of pathogen-specific immune responses in HIV-infected patients during the first months of HAART. The observed clinical deterioration (infectious disease complication) may represent a response to high antigen burden, excessive response of a recovering immune system, exacerbated pro-inflammatory cytokine response, or a dysregulated immune response due to the inability to generate regulatory mediators.19 Evidence for early recovery of mycobacterial-specific immunity in children previously vaccinated with neonatal BCG and exposed to Mycobacterium tuberculosis was demonstrated in a recent study.20 Reports of BCG complications occurring in HIV-infected children not receiving HAART have predominantly described localized disease manifesting as ulceration of the vaccine site with or without ipsilateral axillary lymphadenitis, and less frequently disseminated forms of disease.8,9 In keeping with the few other reports in the medical literature describing IRIS due to BCG,11–13 the children in this study all developed ipsilateral axillary or extra-axillary lymphadenitis characterized by a marked local inflammatory response and tendency for rapid progression to suppuration. These features may be important elements of a clinical case definition of BCG IRIS. We also identified one suspected case of disseminated BCG disease presenting as IRIS. The incidence of disseminated BCG disease presenting after commencement of HAART in children is not known.

Diagnosis of IRIS due to infectious organisms is dependent on documenting the infectious complication and demonstrating concomitant virological suppression and immune restoration (an increasing CD4 count or percentage). Current case definitions do not include a demonstration of pathogen-specific immune recovery.11,12 In routine clinical practice in high HIV-prevalence settings, resource constraints usually preclude the performance of frequent viral load and CD4 measurements. Therefore, as in the present study, viral load and CD4 measurements are rarely performed at the time of onset of the BCG complication.

Prior to starting HAART, the median CD4 count (0.42 x 10⁸/l) and percentage (12.3%) of children who developed BCG complications indicated severe immunosuppression. There was no association between the risk of

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<td>Aspiration/incision and drainage of abscess only</td>
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<tr>
<td>Anti-mycobacterial chemotherapy only</td>
<td>4 (19)</td>
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<tr>
<td>Surgical and medical management</td>
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developing BCG complications and CD4 count in the cohort. In children aged 9 months and younger in whom 81% of events occurred, there was a non-significant trend towards a greater likelihood of developing BCG complications in those with lower baseline CD4 counts ($p = 0.104$). The small total number of children in this group ($n = 99$) may account for the failure to show statistical significance. Children with higher log viral load values prior to starting HAART, indicating more rapidly advancing HIV disease, were more likely to develop BCG complications ($p = 0.001$). Young age was an additional independent risk factor for BCG complications after starting HAART.

Due to cost considerations, we were limited to measuring CD4 count and viral load prior to starting HAART and thereafter at 6-monthly intervals. Measurements were not routinely performed at the time that BCG complications developed. Comparison of baseline and 6-month CD4 counts, viral loads, and WAZ indicated that the majority of children with BCG complications experienced significant improvement after 6 months of HAART, supporting the diagnosis of BCG IRIS. One 7-month-old infant who presented with spontaneous discharge of pus from an axillary abscess (from which $M. \text{bovis}$ BCG was isolated) 14 days after starting HAART, had additional laboratory measurements performed at 6 and 12 weeks on HAART. In this child, the CD4 count had more than doubled after 6 weeks on HAART (0.171 × 10^9/l at baseline; 0.491 × 10^9/l at 6 weeks), and viral load decreased by 2.8 log by 6 weeks and was <400 copies/ml by 12 weeks on HAART. This improvement in immune function and virological indices strongly suggests that the suppurative BCG lymphadenitis was caused by IRIS. Deterioration in clinical and laboratory parameters after 6 months on HAART in a few children did not necessarily exclude IRIS as a cause for their BCG complications. Deterioration several months after the onset of the BCG complication may have been caused by a number of factors including HIV disease progression as a result of BCG disease, pharmacokinetic interaction between rifampin and HAART resulting in sub-therapeutic serum concentrations of antiretroviral drugs and treatment failure, poor adherence to HAART, and development of HIV resistant mutations.

There was no consistency in the treatment of the children in the present study. Suspected or proven disseminated BCG disease should be treated with anti-mycobacterial agents, although the outcome with underlying cellular immunodeficiency is frequently poor.21 Our patient with suspected disseminated BCG disease developing after starting HAART responded well to anti-mycobacterial therapy. Whether local or regional BCG complications in children on HAART should routinely receive anti-mycobacterial therapy is unresolved.6,22 This question requires interrogation through a randomized control trial. Local surgical intervention is probably required for severe complications particularly for fluctuant adenitis, fistulation, and possibly for lymph nodes >1.5 cm in diameter. However, optimal surgical approaches require further investigation.14

This study has certain important limitations. It was hospital-based, which may have resulted in increased identification and reporting of adverse events by both caregivers of the children and clinicians, and thereby an overestimate of the true incidence of BCG adverse events occurring in children after starting HAART across the whole community. The retrospective nature of the study means that there was no standardized system for reporting, investigating, or managing BCG adverse events and this limits the ability to analyze diagnostic approaches and outcomes.

Despite these inherent limitations, we recommend that HIV-infected infants and young children who received BCG vaccination prior to commencing HAART should be closely monitored for BCG complications particularly during the initial 3–6 months on treatment. Rapidly-enlarging or fluctuant regional lymphadenitis should be managed with aspiration or surgical incision and drainage.8,14,22 Mycobacterial culture of pus obtained from lymph nodes, as well as mycobacterial blood culture if available, followed by differentiation of $M. \text{bovis}$ BCG from $M. \text{tuberculosis}$ complex, should ideally be performed to confirm the diagnosis and identify disseminated BCG infection. Suspected or confirmed disseminated disease should be treated with anti-mycobacterial chemotherapy. $M. \text{bovis}$ BCG is inherently resistant to pyrazinamide and this drug should not be used.21 Liver functions should be closely monitored. Pharmacokinetic interactions of rifampin with non-nucleoside reverse transcriptase inhibitors and protease inhibitors may potentially result in sub-therapeutic serum concentrations of antiretroviral drugs that may lead to antiretroviral treatment failure. The antiretroviral regimen should therefore be reviewed and appropriately modified.

In conclusion, while contributing to information on the prevalence and risk factors for BCG complications in HIV-infected children on HAART, this study has identified the need for a clinical case definition of BCG IRIS independent of laboratory parameters for use in resource-limited settings. Furthermore, the role of inexpensive measures to treat the majority of local or regional complications should be rigorously evaluated.

Conflict of interest: No conflict of interest to declare.

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References


