Tacrolimus ointment does not affect the immediate response to vaccination, the generation of immune memory, or humoral and cell-mediated immunity in children

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ORIGINAL ARTICLE

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Background: Concern exists that the prolonged application of immunomodulators to treat atopic dermatitis may cause systemic immunosuppression.
Aims: In a 7-month, multicentre, randomised, controlled trial, we investigated the equivalence of response to vaccination against meningococcal serogroup C disease with a protein-conjugate vaccine in children (2–11 years) with moderate to severe atopic dermatitis, by applying either 0.03% tacrolimus ointment (TAC-O; n = 21) or a hydrocortisone ointment regimen (HC-O; n = 111).
Methods: TAC-O was applied twice daily (bid) for 3 weeks, and thereafter daily until clearance. 1% hydrocortisone acetate (HA) for head/neck and 0.1% hydrocortisone butyrate ointment for trunk/limbs was applied bid for 2 weeks; thereafter HA was applied bid to all affected areas. At week 1, patients were vaccinated with protein-conjugate vaccine against meningococcal serogroup C, and challenged at month 6 with low dose meningococcal polysaccharide vaccine. The control group (44 non-atopic dermatatits children) received the primary vaccination and challenge dose. Assessments were made at baseline, weeks 1 and 5, and months 6 and 7. The primary end point was the percentage of patients with a serum bactericidal antibody (SBA) titre ⩾8 at the week 5 visit.
Results: The response rate (patients with SBA titre ⩾8) was 97.5% (confidence interval (CI) approximately 97.3 to 100), 99.1% (94.8 to 100) and 97.7% (93.3 to 100) in the TAC-O, HC-O and control groups, respectively.
Conclusions: The immune response to vaccination against meningococcal serogroup C in children with atopic dermatitis applying either 0.03% TAC-O or HC is equivalent. Ointment application does not affect the immediate response to vaccination, generation of immune memory or humoral and cell-mediated immunity.

Atopic dermatitis is a chronic, pruritic, inflammatory skin disease that can seriously affect the health and quality of life of the patient. Intense itching is the predominant symptom and excessive scratching can cause damaging excoriations, erosions and lichenification of the skin.[1] The disease is most common during childhood, with 80–90% of children having onset before 5 years of age,[2] and is likely to persist into adulthood in those who are severely affected.[3] The exact pathogenesis of atopic dermatitis is unknown, but it is recognised that T cell-mediated reactions[4] and increased eosinophil levels[5] are involved in the inflammatory response.

Atopic dermatitis usually has a relapsing course, and requires long-term continuous or intermittent treatment. Emollients provide symptomatic relief by reducing the intense itching and inflammation. However, for the treatment of acute exacerbations, most patients require topical treatment with either corticosteroids or calcineurin inhibitors such as tacrolimus or pimecrolimus. Children with moderate to severe atopic dermatitis have large affected body surface areas, often with open and weeping lesions, and this raises concerns that the prolonged application of topical immunomodulators may cause systemic immunosuppression. Current evidence is that the percutaneous absorption of tacrolimus and pimecrolimus is minimal.[6–9] Nonetheless, as atopic dermatitis often occurs in young children who are undergoing childhood immunisation programmes, it is important to determine whether topical immunomodulators have an effect on the humoral and cell-mediated immune response to vaccination.

Information about the immune response to vaccination of patients with atopic dermatitis treated with topical immunomodulators is scarce. Several studies, however, have investigated the immune response to vaccination of children with corticosteroid-dependent asthma. It seems that children receiving short-term low to moderate daily maintenance doses of systemic corticosteroids can receive live virus vaccines without marked suppression of the antibody response.[10] Hanania *et al*[11] found that children with asthma receiving high-dose inhaled corticosteroids had a normal response to A antigens of the inactivated influenza vaccine. Other studies on children with asthma found no association between inhaled corticosteroid use and varicella vaccine failure,[12] or an impaired immune response to pneumococcal vaccines.[13] With regard to children with atopic dermatitis applying topical immunomodulators, Papp *et al*[14] reported that treating children with 1% pimecrolimus cream for up to

Abbreviations: SAE, serious adverse event; SBA, serum bactericidal antibody; TAC-O, tacrolimus ointment

Table 1 Demographics and baseline characteristics of the per-protocol population

	HC regimen (n = 111)	0.03% TAC-O (n = 121)	Control (n = 44)
Age (years)			
Mean (SD)	6.0 (3.1)	6.2 (3.1)	7.3 (2.3)
Min–max	2–11	2–11	2–11
Sex, n (%)			
Male	47 (42.3)	58 (47.9)	27 (61.4)
Female	64 (57.7)	63 (52.1)	17 (38.6)
Ethnic group			
White	106 (95.5)	116 (95.9)	44 (100.0)
Black	1 (0.9)	0 (0.0)	0 (0.0)
Oriental	2 (1.8)	2 (1.7)	0 (0.0)
Other	2 (1.8)	3 (2.5)	0 (0.0)
Severity of AD on day 1, n (%)			
Moderate (4.5–7.5)	64 (57.7)	77 (63.6)	NA
Severe (8–9)	47 (42.3)	44 (36.4)	NA
Total affected body surface area (%), day 1—median (min–max)	32.0 (2–100)	27.0 (1–100)	NA

AD, atopic dermatitis; HC, hydrocortisone; max, maximum; min, minimum; NA, not applicable. TAC-O, tacrolimus ointment

2 years did not affect the seropositivity rates for tetanus, diphtheria, measles or rubella after vaccination. In a small US study of 23 children with atopic dermatitis, the application of 0.03% tacrolimus ointment (TAC-O) for 7 weeks had no effect on the serological response to pneumococcal polysaccharide vaccine.[15]

To increase our knowledge of the immune response to vaccination of children with atopic dermatitis treated with topical immunomodulators, we investigated whether the application of a hydrocortisone regimen or 0.03% TAC-O had any effect on the immune response after vaccination against meningococcal serogroup C disease.

METHODS

Study design

This was a 7-month, randomised, double-blind, comparator-controlled, clinical trial conducted in 27 centres in seven European countries and 10 centres in Australia. The study was conducted in accordance with the ethical principles described in the Declaration of Helsinki, and the ethics committee of each centre reviewed the protocol and granted approval before the study began. Assessments were conducted at baseline (day 1, treatment allocation) and at weeks 1 and 5, and months 6 and 7.

Patients

After receiving written informed consent from the patient's legal representative or the patient, children aged 2–11 years diagnosed with atopic dermatitis on the basis of the criteria of Hanifin and Rajka[16] were enrolled in the study. The patients were required to have a grading of moderate to severe atopic dermatitis (ie, score at least 4.5) as defined by the scoring system of Rajka and Langeland.[17]

Children aged 2–11 years who did not have atopic dermatitis were enrolled to form the control group.

Table 2 Day of last ointment application for the per-protocol population

	HC regimen (n = 111)	0.03% TAC-O (n = 121)
n	108	119
Mean	166.8	185.1
SD	65.17	55.74
Min	33	19
Median	195.5	210
Max	252	239

HC, hydrocortisone; max, maximum; min, minimum; TAC-O, tacrolimus ointment.

For the two groups of patients with atopic dermatitis, randomisation was 1:1, stratified by centre and generated by the study sponsor. The sponsor's clinical trial packaging department prepared blinded treatment boxes and tubes that could be identified only by patient number. Labels detailing lot numbers and expiry date were identical for all ointment tubes. The investigator reviewed the patient's diary card at weeks 1 and 5 to assess compliance with the study treatment.

Treatment

Patients with atopic dermatitis applied 0.03% TAC-O twice daily for 3 weeks (morning and evening). Thereafter, TAC-O was applied once daily until clearance (ie, absence of itching); vehicle ointment formed the second daily application so as to maintain blinding. Patients in the hydrocortisone group applied 1% hydrocortisone acetate ointment to the head and neck, and 0.1% hydrocortisone butyrate ointment to the trunk and limbs twice daily for 2 weeks. Thereafter, 1% hydrocortisone acetate was applied twice daily to all affected body areas until clearance.

Treatments prohibited during the study included other topical corticosteroids for the treatment of atopic dermatitis, systemic corticosteroids, ultraviolet light treatment (UVA, UVB), systemic non-steroidal immunosuppressants and other topical immunomodulators (eg, pimecrolimus). The washout phase for these treatments was 4 weeks for UVA and UVB, 2 weeks for systemic non-steroidal immunosuppressants, 5 days for systemic corticosteroids and 3 days for topical corticosteroids and immunomodulators.

None of the controls had atopic dermatitis, and therefore these children received no treatment with ointment.

Patients with atopic dermatitis and controls were vaccinated with a protein-conjugate vaccine against meningococcal serogroup C at week 1 (Meningitec, Wyeth Pharmaceutica, Hants, UK), and challenged with a low dose of meningopolysaccharide vaccine at month 6 (AC VAX, SmithKline Beecham Biologicals, Rixensart, Belgium).

Assessments

Meningococcal C conjugate vaccines produce high levels of serogroup C-specific immunoglobulin (Ig)G antibodies and serum bactericidal antibody (SBA) activity that provide immune protection against serogroup C meningococcal disease.[18 19] The primary end point of this study was the percentage of patients who at the week 5 visit had an SBA titre ≥ 8, which is an accepted correlate of protection.[20]

The change in serogroup C-specific IgG avidity over time is a useful marker of priming for immunological memory

Table 3 Patients (n (%)) in the per-protocol population with serum bactericidal antibody titre ⩾8 at the week 5 visit

	HC regimen (n = 111)	0.03% TAC-O (n = 121)	Control (n = 44)
Week 5 response rate	110 (99.1)	118 (97.5)	43 (97.7)
95% CI, approximation	97.3 to 100	94.8 to 100	93.3 to 100
95% CI, Wilson score	95.1 to 99.8	93.0 to 99.2	88.2 to 99.6

HC, hydrocortisone; TAC-O, tacrolimus ointment.
Difference in response rate (TAC-O–HC ointment group) at week 5 = −1.6; 95% CI, approximation = −4.9 to 1.7; 95% CI Newcombe–Wilson = −6.2 to 2.8.

because it indicates a T cell-dependent antibody response.[21 22] Therefore, a secondary end point of the study was the measurement of serogroup C-specific IgG antibody avidity. Additional secondary end points included measurement of Ig levels (meningococcal serogroup C-specific IgG, total IgG and IgG subclasses, IgM, IgA, IgE) and lymphocyte subsets (CD3, CD4, CD8, CD19).

Assays for SBA, meningococcal serogroup C-specific IgG and antibody avidity were carried out as previously described.[21]

Clinical efficacy was measured by the physician's global evaluation of clinical response and assessments of affected body surface area. Safety was assessed by the monitoring of adverse events reported by the parent or observed by the investigator. An adverse event was defined as any untoward occurrence in a patient during the study, regardless of whether it was related to the study treatment.

Statistical analyses

Sample size was calculated according to the published method for clinical trials.[23] It was assumed that with a response rate of 75% in the hydrocortisone and TAC-O groups, a δ of 20% and a significance level of 5%, a sample size of 100 patients per treatment group would be needed to show equivalence with a power of 90%. To account for protocol violations and possible early withdrawals from the study, 125 patients were randomised to each treatment group.

The full analysis population comprised all patients who received at least one application of study ointment and were vaccinated against meningococcal serogroup C. This population was used for the clinical efficacy assessments. For the analysis of the primary end point and all other immunological parameters, the per-protocol population was used—that is, all randomised patients who were compliant with the study protocol before the primary end point assessment. The safety population included all patients who received at least one application of study ointment.

The primary end point was analysed by calculating two-sided 95% confidence intervals (CIs) using the Newcombe Wilson Score Method.[24] Fisher's exact test was used to compare the incidence of adverse events between the two groups of patients with atopic dermatitis.

RESULTS

As the per-protocol population was the primary analysis set for the immunological parameters, only data related to these patients are described unless otherwise stated. In total, 232 patients formed the per-protocol population (111 patients in the TAC-O group and 121 patients in the hydrocortisone group) and 44 patients formed the control group. The patient groups were comparable with respect to demographic and baseline characteristics (table 1).

More patients in the hydrocortisone group discontinued the study prematurely (n = 20; 18.0%) compared with those in the TAC-O group (n = 13; 10.7%) and the control group (n = 2; 4.5%). Lack of efficacy was the main reason for discontinuation in the hydrocortisone group (n = 8; 7.2%). The main reasons for discontinuation in the TAC-O group were lack of efficacy (n = 3; 2.5%) and ineffectiveness of vaccination (n = 3; 2.5%). In the control group, one child (2.3%) discontinued the study because the vaccination was not effective, and another child discontinued because there was no challenge dose at month 6. Duration of the study was comparable among treatment groups. Patients in the hydrocortisone, TAC-O and control groups remained in the study for a median of 213, 215 and 216 days, respectively.

Ointment usage

Adherence to treatment was good: 100% adherence in the hydrocortisone group and 99.2% in the TAC-O group at week 5. Median (minimum–maximum) total ointment usage in the hydrocortisone group between day 1 and week 5 was 86 g (5–308 g) hydrocortisone acetate and 42 g (0–76 g) hydrocortisone butyrate. In the tacrolimus group, 79 g (0–366 g) TAC-O and 19 g (0–150 g) vehicle ointment were applied during the same period. Most patients applied ointment either continuously or intermittently throughout most of the study period (an average of 166 days in the hydrocortisone group and 185 days in the tacrolimus group; table 2).

SBA titre

Both groups of patients with atopic dermatitis had a high response rate at week 5, and there was no difference between groups in the percentage of patients with an SBA titre ⩾8 (table 3). Equivalence was observed: the two-sided 95% CI for the difference between the two treatment groups with atopic dermatitis (tacrolimus−hydrocortisone) was (−6.2 to 2.8), which was within the prespecified equivalence margin of (−20 to 20). The response rate of the children in the control group was similar to that of the children with atopic dermatitis.

At month 6, the number (percentage) of patients with an SBA titre ⩾8 was 77 (93.9%), 88 (92.6%) and 36 (97.3%) for the hydrocortisone, TAC-O and control groups, respectively. The respective values, post-challenge, at month 7 were 88 (100%), 101 (99.0%) and 36 (100%).

Table 4 Meningococcal serogroup C-specific immunoglobulin G data (geometric mean) for the per-protocol population

	HC regimen (95% CI) (n = 111)		0.03% TAC-O (95% CI) (n = 121)		Control (95% CI) (n = 44)	
Day 1	111	0.16 (0.13 to 0.20)	120	0.19 (0.15 to 0.24)	44	0.13 (0.10 to 0.17)
Week 5	111	16.2 (12.8 to 20.4)	121	12.5 (10.0 to 15.6)	44	15.0 (11.3 to 20.1)
Month 6	83	2.7 (2.0 to 3.7)	96	2.9 (2.2 to 3.8)	38	2.5 (1.8 to 3.3)
Month 7	89	9.7 (7.4 to 12.7)	104	9.7 (7.8 to 12.1)	38	7.2 (5.6 to 9.3)

HC, hydrocortisone; TAC-O, tacrolimus ointment.

Table 5 Incidence of the most common* adverse events assessed to be causally related† to the study drug for the safety population

Primary system organ class preferred term	HC regimen (n = 124), n (%)	0.03% TAC-O (n = 133), n (%)	p Value‡
General disorders and administration site conditions			
Application site burning	2 (1.6)	10 (7.5)	0.036
Application site erythema	3 (2.4)	2 (1.5)	0.675
Application site pruritus	4 (3.2)	8 (6.0)	0.380
Application site rash	0 (0.0)	3 (2.3)	0.499
Pain NOS	0 (0.0)	2 (1.5)	
Infections and infestations			
Application site infection	2 (1.6)	0 (0.0)	0.232
Eczema infected	2 (1.6)	2 (1.5)	1.000
Skin and subcutaneous tissue disorders			
Dermatitis atopic aggravated	14 (11.3)	5 (3.8)	0.030
Pruritus	3 (2.4)	2 (1.5)	0.675
Rash NOS	4 (3.2)	1 (0.8)	0.200

HC, hydrocortisone; NOS: not otherwise specified (MedDRA term); TAC-O, tacrolimus ointment.
*At least 1% of patients; †Causally related to study drug is defined as highly probable, probable, possible or not assessable, or missing relationship; ‡Fisher's exact test.

Geometric means for SBA titre were high at week 5, decreased by month 6 and increased again at month 7 in all the three groups (fig 1). There was no difference between the two groups of patients with atopic dermatitis at any point during the study, or between the patients with atopic dermatitis and the children in the control group.

Other immunological parameters

Ig levels for meningococcal serogroup C-specific IgG immediately increased after primary vaccination, decreased with time and increased again after challenge with the low-dose meningococcal polysaccharide vaccine (table 4).

Figure 2 shows that the antibody avidity indices increased during the study in all three groups of children between week 5 and month 6, and again between months 6 and 7; this is evidence of a T cell-dependent antibody response after vaccination. We found no differences among the groups at any time point.

Analysis of the IgG data over time showed that median levels of total IgG and median IgG subclasses were similar for all three groups and within the normal reference ranges. In addition, median levels of IgA and IgM were comparable for all three groups, and within the normal reference ranges. Only IgE levels, as would be expected, were higher in patients with atopic dermatitis than those in the control group.

Median levels of the absolute counts of the various lymphocytes did not differ among groups, were stable over time and were within the normal reference ranges.

Clinical improvement

Patients with atopic dermatitis in both treatment groups experienced substantial clinical improvement during the study. With respect to the physician's global evaluation of clinical response, by week 5, more patients in the TAC-O group experienced clearance or excellent improvement compared with the patients applying the hydrocortisone regimen (41.1% *v* 29.8%). The median percentage of affected total body surface area at week 5 was 11.5% in the TAC-O group and 5.6% in the hydrocortisone group ($p = 0.007$, Wilcoxon rank sum test).

Adverse events

The safety population comprised 124 patients in the hydrocortisone group and 133 and 50 patients in the TAC-O and control groups, respectively. Altogether 97 (78.2%) patients, 100 (75.2%) patients and 32 (64.0%) patients in the hydrocortisone, TAC-O and control groups reported adverse events during the study. Patients applying TAC-O had considerably more skin burning assessed by the investigator to be causally related to treatment compared with those in the hydrocortisone group ($p = 0.036$; table 5). Patients applying hydrocortisone experienced significantly more causally related aggravated atopic dermatitis ($p = 0.03$). In both groups of patients with atopic dermatitis, most of the causally related adverse events occurred at the site of ointment application.

A few serious adverse events (SAEs) were reported during the study, and the incidence and nature of the SAEs were similar in the hydrocortisone and TAC-O treatment groups.

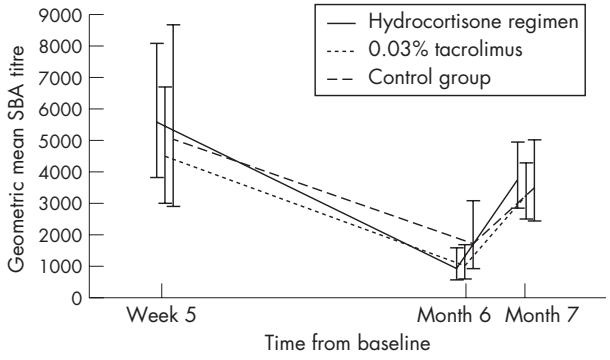

Figure 1 Serum bactericidal antibody (SBA) titre: geometric means and two-sided 95% confidence intervals.

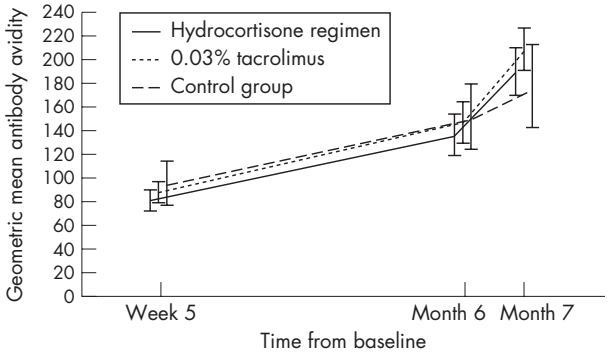

Figure 2 Antibody avidity: geometric means and two-sided 95% confidence intervals.

One case of herpes simplex and one case of asthma were assessed as being ''possibly'' related to TAC-O. In both patients, the SAE resolved after discontinuation of treatment. No causally related SAEs were reported in the hydrocortisone group.

The most common adverse event observed in the control group of children was nasopharyngitis (n = 8, 16.0%), followed by joint pain (n = 3, 6.0%) and otitis media (n = 3, 6.0%). The incidence rate of nasopharyngitis was similar to that seen in the patients with atopic dermatitis.

We found no clinically relevant changes in laboratory values or vital signs throughout the study in any of the patients, and no differences between treatment groups.

DISCUSSION

As there is concern that the prolonged application of topical immunomodulators to patients with atopic dermatitis may cause systemic immunosuppression, the aim of this study was to investigate whether these treatments affect the cell-mediated response to vaccination. These study data clearly showed that the application of either 0.03% TAC-O or hydrocortisone ointment to children with moderate to severe atopic dermatitis did not interfere with the ability of the child to raise protective antibody levels after vaccination against meningococcal serogroup C with a protein-conjugate vaccine. The percentage of patients with atopic dermatitis who had an SBA titre ⩾8 at week 5 after primary vaccination was similar to that of the children without atopic dermatitis. Furthermore, the increases in SBA titre, meningococcal serogroup C-specific IgG and antibody avidity indices between months 6 and 7 provide evidence of the induction of immune memory. As hydrocortisone butyrate is a more potent topical immunosuppressant than 0.03% TAC-O, the indication that even applying a mid-potent corticosteroid twice daily to the trunk and limbs of children for 2 weeks did not affect the immune response to vaccination is reassuring.

The immune response after vaccination against other childhood diseases would probably be similar to that seen in the children in this study who were vaccinated against meningococcal serogroup C. In previous studies on vaccination of children with atopic dermatitis, the seropositivity rates for tetanus, diphtheria, measles or rubella after vaccination were unaffected even after 2 years of treatment with 1% pimecrolimus cream,[14] and in the US study the serological response to pneumococcal polysaccharide vaccine was unaffected by 7 weeks of treatment with 0.03% TAC-O.[15]

The safety profiles of 0.03% TAC-O and the hydrocortisone regimen observed in this study were consistent with those reported previously,[25 26] and gave no reason for concern.

In conclusion, this study shows that after vaccination against meningococcal serogroup C with a protein-conjugate vaccine, there was no difference in immune response between children with atopic dermatitis applying either 0.03% TAC-O or a hydrocortisone ointment and children with no atopic dermatitis. The application of ointments containing immunomodulators does not adversely affect the immediate response to vaccination, the generation of immune memory, or humoral and cell-mediated immunity in childhood.

What is already known on this topic

- Little is known about the effect of applying topical treatments containing tacrolimus or corticosteroids on the immune response to vaccination.
- Topical immunomodulators are currently under review by the US and European health authorities because of the theoretical risk of systemic immunosuppression.

What this study adds

In children, treatment with 0.03% tacrolimus ointment or a hydrocortisone ointment regimen does not adversely affect:

- the immediate response to vaccination
- the generation of immune memory
- humoral and cell-mediated immunity.

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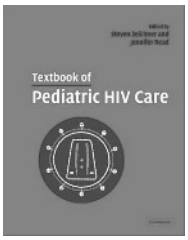
school and residential opportunities for pain management, as well as the chapter on providing pain services in developing countries where these are often unavailable owing to more pressing public health concerns. Also, the consistent emphasis placed on non-pharmacological approaches to pain relief (such as cognitive–behavioural or physical treatments) throughout several chapters points out the essential role that these methods have as complements to our conventional analgesic pharmacopoeia.

This book is not intended as a comprehensive volume on pain management in children, and lacks the practicality of a potential reference text in this field. However, it should appeal to those practitioners who already have a strong interest in pain management and are seeking state-of-the-art information on what is currently being done and explored by experts in their field, and to those who are willing to implement new and creative ways of ''bringing pain relief to children''.

C J Newman

Textbook of pediatric HIV care

Edited by Steven Zeichner, Jennifer Read. Published by Cambridge University Press, Cambridge, 2005, £175.00 (hardback), pp 757. ISBN 0-52182-153-3



Another multiauthor textbook on paediatric HIV. How will it help you when you meet children and families infected with and affected by HIV? It will provide good background information for teaching and personal study, but may be less valuable in managing HIV positive children.

The book aims to provide ''accessible information'' and hopes to become the ''standard reference for clinicians throughout the world''. However, the book mostly focuses on practice in the US (not surprising when all but one of the authors work there).

The book provides some useful background information on HIV and its specific complications. It is well laid out, with many subheadings, and every chapter has an aim at the start. The chapters on virology and post-exposure prophylaxis are useful.

The increasing number of drugs available for children with HIV will make any textbook out of date almost as soon as it is published. This is probably the case here. To try to get round this, links to web-based guidelines are given. However, even the current Paediatric European Network for Treatment of AIDS (PENTA) guidelines (www.ctu.mrc.ac.uk/penta/) are being revised to try to keep up with this rapidly developing area.

The section on drug interactions provides a useful list but does not reference the excellent website from the University of Liverpool (http://www.hiv-druginteractions.org/index.asp).

Improvements needed in a second edition include reference to the landmark HIV Paediatric Prognostic Markers Collaborative Study,[1] recognition that the organism that causes *Pneumocystis carinii* pneumonia is now named *P jiroveci* (not *P carinii*), and contributions from some authors from outside the USA.

This book should be available in paediatric departments that see children with HIV. However, it would be more important for these units to have access to the guidelines on the CHIVA website (www.bhiva.org/chiva) and to have access to expert advice. The recent establishment of a national network for paediatric HIV should make expertise about HIV available to all children who need it in the UK.

A Riordan

Reference

1 **HIV Paediatric Prognostic Markers Collaborative Study Group**. Short-term risk of disease progression in HIV-1-infected children receiving no antiretroviral therapy or zidovudine monotherapy: a meta-analysis. *Lancet* 2003;**362**:160–511.

CORRECTIONS

doi: 10.1136/adc.2006.094276corr1

T Hofman, N Cranswick, P Kuna, *et al*. Tacrolimus ointment does not affect the immediate response to vaccination, the generation of immune memory, or humoral and cell-mediated immunity in children. *Arch Dis Child* 2006;**91**:905–10. A typographical error was introduced into the Aims section of the Abstract of this paper. (TAC-O; n = 21) should read (TAC-O; n = 121). In addition, the second sentence of the results section of the paper should read: In total, 232 patients formed the per-protocol population (121 patients in the TAC-O group and 111 patients in the hydrocortisone group) and 44 patients formed the control group.

doi: 10.1136/adc.2006.0103093corr1

Inwald D P, Yen Ho S, Shepherd M N, *et al*. *Arch Dis Child* 2006;**91**:928.

The name of the third author of this article was spelt incorrectly—the correct spelling is M N Sheppard.

Pre-published book reviews

Book reviews that have been accepted for publication but have not yet been published in the print journal can be viewed online at http://adc.bmjjournals.com/misc/bookreviews.shtml