Abacavir (ABC), a nucleoside reverse transcriptase inhibitor (NRTI), has been shown to be an effective component of combination antiretroviral therapy (ART) regimens for both paediatric and adult patients. South African (SA) national ART treatment guidelines recommend ABC for first- and second-line regimens in paediatric patients aged ≥3 months. Despite demonstrating a durable antiretroviral response, ABC is not a preferred option for first- or second-line adult regimens in SA, primarily due to its relatively high cost, but also due to concerns about toxicity, particularly hypersensitive reactions, although these are only experienced in 4% of individuals receiving ABC. Such reactions commonly present as a rash and fever, but may manifest as fatigue, flu-like symptoms or gastrointestinal upset. Common adverse effects include headache, loss of appetite, nausea and diarrhoea. Of all nucleoside reverse transcriptase inhibitors (NRTIs), ABC is associated with the lowest rate of mitochondrial dysfunction, including lactic acidosis, peripheral neuropathy and lipatrophy. Substitution of stavudine (d4T) with ABC improves mitochondrial indices, reduces adipocyte apoptosis, and has been shown to be superior to substitution with zidovudine (ZDV) in adults. In older children, once-daily use of ABC has also been shown to be effective, facilitating adherence and improving patient satisfaction.

ABC-containing regimens are used in adult cases where standard first- and second-line treatments have either failed or cannot be tolerated. Given current national guidelines for limited inclusion of ABC in highly active ART (HAART) regimens, use of the drug among HIV-positive adults eligible for treatment is generally expected to be low. In 2011, however, a higher than anticipated use of ABC was observed across all provinces of SA. Actual use outpaced the projected need for the drug, placing strains on supplies and programme budgets. In response to concerns about the unnecessary use of ABC (300 mg), we investigated current prescribing of the drug to adults and children accessing ART in public sector programmes across Gauteng Province, South Africa. ABC was almost exclusively prescribed to children initiating ART and adults requiring regimen changes due to drug toxicities. Patterns of ABC use among HIV-positive paediatric patients followed national ART treatment guidelines on the application of the drug. Although ABC is commonly used in the private sector for adults, the current national ART treatment guidelines for adults and adolescents should include ABC as an alternative to standard first- or second-line ART.
Results

Of 23 084 patients, 76% (22 089) were adults and 5% (995) were children and adolescents (aged <18 years), reflecting that the HIV clinics were mainly adult-oriented. The majority of patients attending the central-JHB (12 120/12 185; 99.5%), west-JHB (1 875/2 267; 82.7%) and east-JHB (2 705/2 773; 97.5%) clinics were adults aged >18 years. TLC had a small cohort of paediatric (<10 years) and adolescent (10 - 18 years) patients (65/12 185; 0.5%), compared with north-JHB, where paediatric/adolescent (470/5 859; 8.0%) and adult HIV-positive patients (5 389/5 859; 92%) were seen separately (Table 1).

The total number of patients receiving ABC was 619/23 084 (2.7%). An estimated 0.9% (206/22 089) of adults attending the 4 sites were prescribed ABC-containing regimens at the time of the study, compared with 42% (413/995) of paediatric/adolescent patients (≤18 years). Among patients aged ≤18 years, 11% (7/65), 54% (254/470), 33% (128/392) and 35% (24/68) were receiving ABC-containing regimens at the central-, north-, west- and east-JHB clinics, respectively. At the west- and east-JHB clinics, nearly all patients receiving ABC (98%; 128/131 and 96%; 24/25, respectively) were aged ≤18 years. The number of adults receiving ABC varied from 2.3% (3/131) in west-JHB, to 4% (1/25) in east-JHB, 27% (95/349) in north-JHB and 94% (107/114) in central-JHB. Despite the small size of some cohorts, the results demonstrated a variation in the number of adults prescribed ABC at these 4 clinics.

Among paediatric and adolescent patients (aged ≤18 years), median time receiving ART and ABC varied by clinic. The TLC paediatric/adolescent population had a median duration on ART of 91 months (IQR 40 - 94 months) compared with 37 months (IQR 24 - 51) at the north-JHB clinic and 6 months at both the west-JHB (IQR 3 - 27 months) and east-JHB (IQR 2 - 8 months) clinics. A longer median duration of ART was associated with longer time receiving ABC, with paediatric/adolescent patients at TLC prescribed the drug for a median 40 months (IQR 20 - 94 months). The median time on ABC was shorter at the north-JHB (13 months; IQR 6 - 24 months), west-JHB (5 months; IQR 2 - 8 months) and east-JHB clinics (5 months; IQR 2 - 6 months). More than half of the paediatric/adolescent patients at TLC (4/7; 57%) and the north-JHB clinic (129/254; 51%) had been receiving ABC for longer than 12 months. Among adult patients receiving ABC at the clinics at the time of the study, 35% (TLC; 37/107) and 73% (north-JHB; 69/95) had been receiving the drug for longer than 1 year. Only 6% (8/128) of patients attending the west-JHB clinic were prescribed ABC for longer than 12 months. The majority of adult patients prescribed ABC at the time of the study were switched onto the drug from other regimens, with only 18% (19/107) of adult patients at TLC and 28% (27/95) of adult patients at north-JHB clinic initiated on an ART regimen containing ABC. Among adult patients reporting a reason for switching to ABC from another regimen (52%; 81/156), the most common reasons were peripheral neuropathy (17%, 14/81), abnormal fat distribution (28%, 23/81) and toxicity (35%, 28/81). Few specific reasons for switching to an ABC-containing regimen were given for paediatric/adolescent patients (25%, 62/247), but among those cases where a reason was reported, abnormal fat distribution was the leading cause of regimen change (76%, 47/62).

Discussion

When considering sites where both adults and children are routinely treated with ART, ABC is primarily prescribed to children. At the east- and west-JHB clinics, the drug was almost exclusively provided to patients aged ≤18 years. We demonstrated a high variation in the prescription of ABC to adult and paediatric/adolescent patients at the 4 sites across Gauteng Province. While we did not demonstrate dramatic over-use of the drug, 67% of patients receiving ABC were children, consistent with guidelines, while 33% were adults, as a likely result of being switched to ABC from another ART regimen due to adverse effects or toxicity.

However, approximately 23% (46/202) of adults at central- and north-JHB were initiated on an ABC-containing regimen. A large proportion of ABC users at the north-JHB clinic (73%; 254/349) were paediatric/adolescent patients compared with a smaller proportion (27%; 95/349) of adults, yet still less than 2% (95/5 859) of patients aged ≥18 years were on an ABC-containing regimen. A large proportion of these adult patients receiving ABC reported long-term use of the drug (73% for 1 year or longer). The large number of adult patients receiving ABC at the north-JHB clinic was likely related to being switched onto ABC from another ART regimen due to an adverse effect (i.e. peripheral neuropathy, lactic acidosis or lipatrophy/lipodystrophy) – less than 30% of patients aged ≥18 years were initiated on an ABC-containing regimen.

The majority of paediatric/adolescent patients (<80%) at the north-JHB clinic were switched onto an ABC-containing regimen, with 19% (39/201) being due to abnormal fat redistribution. Once-daily use of ABC has been shown to be effective in older children, thereby facilitating adherence and improving patient satisfaction; and it is therefore possible that specialist paediatricians at north-JHB might have prescribed/Switched adolescents to ABC for adherence issues.29,30 Twenty-one per cent of paediatric/adolescent patients were initiated on an ABC-containing regimen. A large proportion of these patients reported long-term use of the drug, with 51% (129/254) receiving ABC for longer than 1 year. This is likely due to the ageing paediatric population receiving care which has maintained paediatric regimens even after moving into adolescence (age 10 - 18 years).

Conversely, <1% (107/12 120) of adults at TLC were receiving ABC, only 35% (37/107) of whom had received the drug for longer than 1 year. Adults were unlikely (17.8%; 19/107) to be initiated on an ABC-containing regimen but rather switched to such a regimen due to toxicity (82.2%; 88/107). The CD4 count (267 cells/mm³; IQR 160 - 392) and proportion with a detectable viral load (13%; 10/80) at the initiation of ABC confirmed that adults patients were most likely switched to ABC rather than initiated on the drug. TLC treated few patients aged <18 years (0.5% of total patients); however, 71% (5/7) of paediatric/
Table 1. Current use of abacavir (300 mg) at 4 Right to Care-supported sites across Johannesburg, Gauteng Province, South Africa

<table>
<thead>
<tr>
<th>Site</th>
<th>&gt;18 years</th>
<th>≤18 years</th>
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<tbody>
<tr>
<td>Themba Lethu Clinic – central JHB (N=12 185)</td>
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<td>7 (11%)</td>
</tr>
<tr>
<td>North JHB (N=5 859)</td>
<td>349 (6.0%)</td>
<td>254 (54%)</td>
</tr>
<tr>
<td>West JHB (N=2 267)</td>
<td>131 (6.0%)</td>
<td>128 (33%)</td>
</tr>
<tr>
<td>East JHB (N=2 773)</td>
<td>25 (0.9%)</td>
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</table>

**Patient demographics and clinical characteristics**

**Gender**
- Male, n (%) 47 (44)
- Female, n (%) 60 (56)

**Age at initiation (years), median (IQR)**
- >18 years 42.2 (34.9 - 51.0)
- ≤18 years 21.0 (18.8 - 24.8)

**Baseline CD4 (cells/mm³), median (IQR)**
- >18 years 78 (31 - 171)
- ≤18 years 10.7 (8.8 - 12.5)

**Time receiving ART (months), median (IQR)**
- >18 years 31.3 (14.3 - 59.5)
- ≤18 years 90.9 (39.8 - 94.3)

**Baseline BMI (kg/m²), median (IQR)**
- >18 years 7.2 (3.5 - 13.6)
- ≤18 years 2.8 (1.0 - 5.7)

**Baseline haemoglobin (g/dl), median (IQR)**
- >18 years 10.7 (8.8 - 12.5)
- ≤18 years 10.7 (8.8 - 12.5)

**Baseline CD4 percentage at start of ABC,* median (IQR)**
- >18 years 78 (31 - 171)
- ≤18 years 10.7 (8.8 - 12.5)

**Detectable viral load (>400 copies/ml) at start of ABC,* n/N (%)**
- >18 years 10/80 (13)
- ≤18 years 1/7 (14)

**Weight at start of ABC (kg),* median (IQR)**
- >18 years 56 (50 - 66)
- ≤18 years 19/107 (17.8)

**Time receiving ABC (months), median (IQR)**
- >18 years 8.5 (4.4 - 16.3)
- ≤18 years 37 (35)

**Initiated on ABC, n (%)**
- >18 years 19/107 (17.8)
- ≤18 years 2/7 (28.6)

**Switched onto ABC, n (%)**
- >18 years 88/107 (82.2)
- ≤18 years 2/7 (28.6)

**Reason for switching,** n
- Virological failure 2
- Clinical progression 1
- Abnormal fat redistribution 5
- Peripheral neuropathy 2
- Toxicity (predominantly kidneys) 10
- Anaemia 4
- Hyperlactataemia/lactic acidosis 1
- Toxicity 12
- More effective drug/interaction 2
- Pregnancy 1
- Other/not specified 48

ABC = abacavir; JHB = Johannesburg. *Within 90 days of ABC initiation. †ABC initiated between April 2004 and August 2011.
adolescent patients on an ABC-containing regimen were initiated on such a regimen. Differences in ABC use across clinics possibly also partially reflect differences in clinical practice. More than 50% of children from the north-JHB clinic were receiving ABC for longer than 1 year, compared with 16% and 0% at west- and east-JHB, respectively. This could be a reflection of advice and recommendations concerning treating ART side-effects, from specialist paediatric HIV physician services available at north-JHB clinic (not available at the other sites). This advice might have included switching from stavudine- to ABC-containing regimens before implementation of the new national ART treatment guidelines. The switching of many children to ABC at north-JHB (79.1%; 201/254) before implementation of the national guideline could explain the perception of high consumption of this drug in JHB.

The majority (79%) of children from the north-JHB clinic were switched onto ABC from another regimen, while 69% and 83% of children from west- and east-JHB, respectively, were initiated onto ABC. This likely reflects the implementation of the 2010 SA national ART treatment guidelines at these 2 sites, which recommend that infants and children be initiated on a regimen of ABC and lamivudine (3TC) plus lopinavir/ritonavir (LPV/r) or efavirenz (EFV). Among paediatric and adolescent patients, the most frequent reason for switching onto an ABC-containing regimen was ART toxicity and side-effects, most commonly abnormal fat redistribution. This highlights the toxicity of NRTIs, particularly d4T, didanosine (ddI) and zidovudine (AZT), even in children.7

The majority of adults prescribed ABC at the time of the study had been switched onto the drug from other regimens. Specified reasons for prescribing ABC to these adults were largely related to ART toxicity and side-effects, including renal toxicity, anaemia, peripheral neuropathy, abnormal fat distribution, and hyperfetataemia or lactic acidosis. This highlights the need to make ABC available to adults and include the drug in the national guidelines for adults as an alternative to standard first- and second-line ART.

Study strengths and limitations

The biggest strengths of this study include the size of the cohort and the depth of the data (using a standardised, electronic data-capturing system, data on ART regimens, visit dates, outcomes, laboratory investigations and demographic data is of high quality). Since these are clinical cohorts, the findings should be considered in light of the study limitations which include missing data (laboratory investigations and reasons for switching) or under-reported conditions or adverse drug effects and the generalisability of the results. This study was done in RTC-supported sites in Johannesburg, thus with a higher level of clinical support and progressive prescription than other sites (i.e. rural sites without any supporting NGO). It is likely that ABC use, especially in adults, would be lower in rural, unsupported sites.

Conflict of interest.

The authors declare that no competing interests exist. Right to Care (RTC) funded part of the research and supported the provision of treatment for the study’s patients.

Acknowledgments.

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References