Adverse drug reactions during drug-resistant TB treatment in high HIV prevalence settings: a systematic review and meta-analysis

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Objectives: To estimate the prevalence of adverse drug reactions or events (ADR) during drug-resistant TB (DR-TB) treatment in the context of settings with high HIV prevalence (at least 20% of patients).

Methods: We conducted a systematic review and meta-analysis of articles in PubMed and Scopus. Pooled proportions of patients experiencing adverse events and relative risk with 95% CI were calculated.

Results: The search yielded 24 studies, all observational cohorts. Ten reported on the number of patients experiencing ADR and were included in the meta-analysis representing 2776 study participants of whom 1943 were known to be HIV infected (70.0%). An average of 83% (95% CI: 82%–84%) of patients experienced one or more ADR. Among the seven articles (n = 664 study participants) with information on occurrence of severe ADR, 24% (95% CI: 21%–27%) of patients experienced at least one severe ADR during drug-resistant TB treatment. Sixteen of the 24 studies analysed the relative risk of ADR by HIV infection, nine of which found no statistically significant association between HIV infection and occurrence of drug-related ADR. There was insufficient information to disaggregate risk by concomitant treatment with HIV antiretrovirals or by immunosuppression (CD4 count).

Conclusions: No randomized clinical trials were found for WHO-recommended treatment of drug-resistant TB treatment where at least 20% of the cohort was coinfected with HIV. Nearly all patients (83%) experience ADR during DR-TB treatment. While no significant association between ADR and HIV coinfection was found, further research is needed to determine whether concomitant antiretrovirals or immunosuppression increases the risks for HIV-infected patients.

Introduction

The WHO estimates that in 2015, 580 000 of the 6.1 million persons who were notified as TB cases had a drug-resistant strain of the disease. Only 20% were diagnosed and initiated on treatment of whom 52% had successful outcomes. Access to drug-resistant TB treatment is limited by timely diagnosis of resistance, availability of treatment, staff capacity, high early mortality and cost.

Patients resistant to rifampicin alone or in combination with any other first-line or second-line drugs require second-line treatment. Rifampicin-resistant (RR) TB includes MDR-TB, resistant to both isoniazid and rifampicin, and XDR-TB, MDR-TB that is also resistant to both a fluoroquinolone and a second-line injectable drug. The duration of drug-resistant TB treatment is longer than for drug-susceptible TB (typically 9–24 months) and standard regimens for MDR/RR-TB include four to seven drugs with different mechanisms of action, including: oral bacteriostatic drugs; aminoglycoside and cyclic peptide injectables; fluoroquinolones; and newer agents such as bedaquiline and delamanid.

Many of the drugs have known toxicities, especially at the doses and durations required to treat resistant strains of TB and there is limited clinical trial data on dosage and related side effects. As a result, adverse drug reactions or events (ADR) are very common during drug-resistant TB treatment. A systematic review and meta-analysis of published literature through October 2012 found that 57.3% of included patients had experienced at least one type of ADR, including mild to severe events. ADR can lead to the...
clinician or patient interrupting, stopping or reducing the dosage of treatment before completion, and therefore may increase the risk of mortality, treatment failure or death. Either sequelae from the ADR or the untreated TB disease may lead to reduced quality of life. However, the high mortality, risk of transmission and limited alternatives mean that clinicians and patients with drug-resistant TB are left with little choice.

Within the last decade, there has been escalated progress in drug-resistant TB drug development; new treatments are being developed and multiple drugs are entering or are in clinical trials. Knowing whether the rates of ADR experienced in clinical trials for new drugs are of concern requires a better understanding of the base case scenario. Additionally, in efforts to improve treatment outcomes existing drugs such as linezolid (an oxazolidinone) and clofazimine are being re-purposed for drug-resistant TB treatment. Because the drugs have existing regulatory approval for other indications, randomized controlled trials are not required in many settings and available understanding of the potential side effects and optimal doses for the regimens are limited to observational cohorts. Additionally, the sickest patients or those with HIV, advanced HIV or other comorbid conditions are often excluded from clinical trials. For high-prevalence HIV settings, this can limit applicability of clinical trial data to patients coinfected with HIV and other comorbid conditions. Yet, in some settings, particularly sub-Saharan Africa, TB and HIV are inextricably linked. Treatment of HIV and TB coinfection results in high pill burden and potentially increased toxicity. Effective ART regimens include three drugs, and toxicities can be overlapping. HIV infection, even for the ART naive, and particularly for those who have advanced HIV disease or immunosupression may also pose its own risk for ADR.

To understand the association between HIV infection and treatment and the prevalence of ADR during drug-resistant TB treatment, we systematically reviewed and conducted a meta-analysis of peer-reviewed published literature to identify the types, frequencies, severity and seriousness of ADR associated with the pre-2016 WHO-recommended regimens for drug-resistant TB in settings with HIV coinfection of at least 20%.

Methods
A literature search was done in PubMed (inclusive of MEDLINE) and Scopus. The title, abstract and full text were searched for adverse or toxicity or side effects or safety or tolerability AND drug-resistant or multi-drug resistant or second-line treatment or rifampicin-resistant AND tuberculosis or TB AND human immunodeficiency virus or HIV or acquired immune deficiency syndrome or AIDS. No date ranges were set; the search was initially done on 11 February 2016 and then updated on 4 August 2016. Retrieved results were de-duplicated. Conference proceedings and conference abstracts were not included in the search because of limited presentation of results in abstract format. Manuscripts in languages other than English were excluded.

Titles and abstracts were screened and the following were excluded from the articles to be retrieved: opinion pieces, editorials; guidelines; case reports; and studies with no reports of drug-resistant TB treatment, e.g. drug-susceptible TB treatment, laboratory testing, bench research, pharmacokinetic studies, and diagnostic tools, methods or algorithms. Systematic reviews and meta-analyses identified during the screening were not included in this systematic review, but were retrieved and a manual search was done of the references.

If from the title or abstract it was clear that the article did not meet inclusion criteria or if an exclusion criterion was present, the article was excluded from further review. For any abstracts that met inclusion criteria or for which the abstract was not sufficiently detailed to determine eligibility, the full text was retrieved and reviewed. Retrieved full texts were reviewed for inclusion and exclusion criteria (Table S1, available as Supplementary data at JAC Online). Based on the articles retrieved, the included articles were further classified according to whether they reported on only severe (i.e. events that were severe in intensity11) or serious ADR (i.e. death or a life-threatening experience; hospitalization or prolongation of hospitalization; persistent significant disability; or congenital anomaly9), only on one ADR (e.g. hearing loss), or only on the ADR probably related to one drug (e.g. clofazimine). These more limited sub-analyses were analysed separately from studies reporting on multiple drugs, events and of different ADR severity gradings.

If the same cohort was reported in multiple eligible manuscripts, the article with the most information on ADR (if treatment outcome and ADR were described separately) or the most complete follow-up (if interim results and final results) was included. In one case, each article separately reported on one specific ADR and both papers were included in the analyses for those two individual ADR.

Analysis
Available data were extracted related to the number of severe ADR or adverse events during treatment, disaggregated by type of ADR, suspected drug, grading of ADR severity, HIV and ART status of the patient, and whether the ADR led to the drug being stopped, hospitalization or death. Severity was extracted as per categorization within the articles as severe or worse (severe, life threatening or fatal or grades 3–5) or non-severe (mild or moderate or grades 1–2). Extracted ADR included categories for ADR that have known associations with the anti-TB drugs in the WHO pre-2016 regimens, including: gastrointestinal symptoms, ototoxicity, psychiatric disorder, electrolyte imbalance, anaemia, thyroid dysfunction, liver dysfunction, kidney dysfunction, dermatological problems, peripheral neuropathy, arthralgia, cardiac abnormalities (e.g. QT prolongation), systemic symptoms (e.g. fatigue, general malaise) and seizures. Other reactions were captured and described as reported. Bias was not explicitly assessed as the intention was to include observational studies.

Extracted data were captured in MS Access 2013 and then imported to Stata v14 (College Station, TX, USA) for analysis. The Stata function metaprop was used to create forest plots and analysis of the point and CI estimates for the prevalence of ADR out of all patients, as well as disaggregates when possible (sub-analyses). The function metaprop was used as it is based on binomial distribution appropriate for analysing proportions and is less likely to produce unallowable intervals even when the proportions are close to 0 or 1. The Stata function metan was used for sub-analyses to estimate the relative risk of HIV infection for experiencing an ADR.

Results
Across PubMed, Scopus and reference searches, 727 citations were identified (Figure 1), of which 137 were found to be duplicates. Titles and abstracts of the remaining 590 citations were screened for inclusion and exclusion criteria. Fifty-four articles were retrieved for full-text review, at which point 30 more were excluded.

Data were extracted from the remaining 24 articles (Tables S2 and S3), all of which were not randomized and only seven of which were prospective. Analysis was limited by the reported data, which were not consistent across all studies; the studies were further classified as having a diverse scope of ADR included in the reporting (12 studies, n = 2941 patients). Within the articles that had a diverse coverage, eight reported on both the numbers of patients...
experiencing ADR and the total number of ADR experienced and two provided only a count of patients who had experienced an ADR; these 10 studies were included in the meta-analysis of the proportion of patients experiencing an ADR. Two other diverse coverage studies reported on the count of ADR but not the count of patients and were included in sub-analyses. A further 12 studies included only in sub-analyses were those that described only severe (four studies, n = 421 patients) or serious ADR (one study, n = 1390 patients); only the ADR related to a drug of interest (one study, n = 85 patients); or only a particular type of ADR of interest—hypothyroidism (three studies, n = 468 patients), hearing loss (two studies, n = 588 patients) and peripheral neuropathy (one study, n = 246 patients).

Cohorts from eight countries were included (five African countries: Botswana, Ethiopia, Lesotho, Namibia and South Africa; Haiti; India; and the USA). Sixty per cent (15/25) were from South Africa. The median proportion of HIV-infected patients within the studies was (unweighted) 63.4% (IQR: 39.1%–74.4%) of the 4682 participants. Of the 22 studies reporting patients on HIV treatment, the ART coverage of HIV-infected patients was high (median 90.2%, IQR: 70.8%–100%). ART was usually reported as binary (on ART or not on ART). Six studies further classified ART as having been initiated prior to or during MDR/RR-TB treatment, including two that estimated the number of months prior to MDR/RR-TB treatment. Eighteen studies indicated a median CD4 count; the median CD4 count reported was 202 cells/mm³ (IQR: 90–329).

Of the total 6139 drug-resistant TB patients, 10.1% (n = 622) had second-line drug resistance in addition to rifampicin resistance, including XDR-TB. All 10 studies that were not limited to a specific drug or ADR described a drug regimen that included cycloserine or terizidone. The most commonly reported other drugs were pyrazinamide (8/10 studies), amikacin or kanamycin (8/10 studies), ethionamide (8/10), para-aminosalicylic acid (6/10), moxifloxacin (5/10), levofloxacin (3/10) and ofloxacin (2/10).

**Patients experiencing ADR**

For the 10 studies (n = 2776 patients) included in the main meta-analysis (of which 1943 patients were HIV infected), 1725 patients experienced at least one ADR, with a pooled proportion of 83% (95% CI: 82%–84%) out of all patients (Figure 2). Seven studies (n = 664) reported on the number of patients who experienced at least one severe (or worse) ADR during treatment (Figure 3). The proportion of patients experiencing at least one severe or worse ADR ranged from 13% to 43%, with an overall estimate of 24% (95% CI: 21%–27%).

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**Figure 1. Included articles.**
As shown in Figure 4, gastrointestinal-related ADR, including vomiting, nausea and diarrhoea, were the most commonly reported ADR overall, 837/4498 (18.6%) events disaggregated by ADR type. Of the severe events, gastrointestinal-related ADR (151/743 severe events, 20.3%) were also the most commonly reported. Ototoxicity, including hearing loss and tinnitus, was the second most common for all ADR (n = 746, 16.6%) and severe ADR.
(n = 139, 18.7%) as well. Psychiatric events including depression, suicidal ideation and suicide accounted for 13.7% of all ADR reported. For severe ADR, hypothyroidism (n = 118, 15.9%), peripheral neuropathy (n = 69, 9.3%), psychiatric disorders (n = 61, 8.2%), arthralgia (n = 57, 7.7%) and dermatological symptoms (n = 56, 7.5%) were the next most commonly reported events.

Ten studies reported on hearing loss believed to be a result of treatment with the aminoglycosides amikacin and kanamycin; an additional study indicated that hearing was not routinely tested and was therefore excluded from this sub-analysis (Figure S1). The estimated proportion of all patients experiencing any hearing loss across these studies was 36% (95% CI: 34%–38%).

**Reported ADR by suspected drug**

None of the included studies systematically reported on drug(s) suspected to cause the ADR described with the exception of studies addressing a single ADR of interest, e.g. the papers describing hypothyroidism ascribed whether its occurrence was related to the use of para-aminosalicylic acid and/or ethionamide. While there was one paper focused on clofazimine, the described ADR were not attributed to clofazimine. Across the 628 ADR from 12 papers covering 3326 patients that had counts of any, severe or serious ADR associated with (a) specific drug(s), the second-line injectables combined (kanamycin, amikacin and capreomycin) had 273 reports. Para-aminosalicylic acid and/or ethionamide (the studies indicated that it was unknown which of the two was more likely) were implicated in 235 events, and cycloserine/terizidone were mentioned 92 times.

**Relative risk of ADR by HIV infection and HIV treatment**

Sixteen of the reviewed studies included information about the relative risk of ADR by HIV infection, and most used the Pearson χ² test for difference of proportions (Table 1). Nine studies found no statistically significant association between the proportion of patients experiencing any ADR by HIV status. One study found that HIV-infected patients were at a 4-fold higher cumulative hazard of moderate-to-severe ADR (95% CI: 1.5–10.5) compared with HIV-negative patients. A single study reported that HIV-negative patients experienced more severe ADR. Disaggregation of counts of patients experiencing any ADR by HIV status was limited to two studies, and therefore was not tested through the meta-analysis.
Table 1. Relative risk of ADR by HIV status

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>HIV (%)</th>
<th>Relative risk of ADR by HIV status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brust15</td>
<td>2013</td>
<td>81.3</td>
<td>Difference in proportions of ADR experienced not statistically significant for 21 individual ADR tested.</td>
</tr>
<tr>
<td>Charles16</td>
<td>2014</td>
<td>24.5</td>
<td>Difference in proportions of ADR experienced not statistically significant, P=0.185.</td>
</tr>
<tr>
<td>Jacobs18</td>
<td>2012</td>
<td>72.6</td>
<td>HIV-infected patients more likely to have hadd: peripheral neuropathy (P=0.001); psychosis and confusion (P=0.004); hearing loss (P=0.047); and thyroid dysfunction (P=0.001). Difference in proportions of ADR experienced by HIV-infected patients on ART or not on ART not statistically significant, P=0.432.</td>
</tr>
<tr>
<td>Kelly19</td>
<td>2016</td>
<td>74.4</td>
<td>Difference in number of ADR experienced not statistically significant as recorded in interviews (P=0.277) and medical records (P=0.098).</td>
</tr>
<tr>
<td>Modongo20</td>
<td>2015</td>
<td>21.7</td>
<td>Difference in proportions of ADR experienced not statistically significant. HIV infected patients had a higher incidence of peripheral neuropathy (P&lt;0.001).</td>
</tr>
<tr>
<td>O'Donnell21</td>
<td>2013</td>
<td>71.9</td>
<td>Difference in proportions of ADR experienced not statistically significant. Difference in proportions of severe ADR experienced not statistically significant. Difference in proportions of ADR experienced by HIV-infected patients on ART or not on ART not statistically significant. Difference in proportions of severe ADR experienced by HIV-infected patients on ART or not on ART not statistically significant.</td>
</tr>
<tr>
<td>Sagwa22</td>
<td>2014</td>
<td>52.5</td>
<td>Cumulative hazard of moderate-to-severe ADR, HIV-infected HR: 4.0, 95% CI: 1.5–10.5. Additional analysis reported in 201339 no statistically significant difference of proportions for 17 ADR tested, only abdominal pain associated with HIV, P=0.02. Effect modification from HIV in adjusted relative risk analysis for nausea and joint pain.</td>
</tr>
<tr>
<td>Shean24</td>
<td>2013</td>
<td>41.7</td>
<td>Difference in proportions of ADR experienced not statistically significant, P=0.26. Difference in number of ADR experienced not statistically significant, P=0.15. Difference in number of severe ADR experienced not statistically significant, P=0.01. Patients who died were more likely to be HIV infected (P=0.01).</td>
</tr>
<tr>
<td>Burgos27</td>
<td>2005</td>
<td>22.9</td>
<td>Difference in proportions of severe ADR experienced not statistically significant, P=0.520.</td>
</tr>
<tr>
<td>Kvasnovsky28</td>
<td>2011</td>
<td>52.4</td>
<td>HIV-negative patients experienced more severe ADR than HIV-infected patients, difference in proportions P&lt;0.01. Difference in proportions of ADR experienced not statistically significant for HIV-infected patients on ART or not on ART, P=0.33.</td>
</tr>
<tr>
<td>Van der Walt31</td>
<td>2013</td>
<td>39.1</td>
<td>Difference in proportions of serious ADR experienced by ART-naive HIV-infected patients not statistically significant, P=0.083.</td>
</tr>
<tr>
<td>Conradie38</td>
<td>2014</td>
<td>80.9</td>
<td>Incident peripheral neuropathy not associated with HIV, HR: 1.00 (95% CI: 0.35–2.91). Prevalent peripheral neuropathy associated with HIV, HR: 3.21 (95% CI: 1.25–8.22); risk was also associated with duration of exposure to stavudine.</td>
</tr>
<tr>
<td>Harris36</td>
<td>2012</td>
<td>57.0</td>
<td>HIV-infected patients were more likely to experience hearing loss, OR: 3.25 (95% CI: 1.65–6.37).</td>
</tr>
<tr>
<td>Modongo37</td>
<td>2012</td>
<td>63.4</td>
<td>Difference in proportions experiencing hypothyroidism not statistically significant.</td>
</tr>
<tr>
<td>Satti38</td>
<td>2014</td>
<td>65.9</td>
<td>Difference in proportions experiencing hearing loss not statistically significant.</td>
</tr>
<tr>
<td>Satti38</td>
<td>2012</td>
<td>67.6</td>
<td>Difference in proportions experiencing hypothyroidism not statistically significant, P=0.172.</td>
</tr>
</tbody>
</table>

Excluded as all patients were HIV infected: Isaakidis 2012,17 Umanah 201526 and Andries 2013.35

There were more differences by HIV status found in individually reported ADR. Two studies found that HIV was associated with an increased odds of experiencing hearing loss18 for patients on amikacin or kanamycin; and two studies found an association with peripheral neuropathy and either HIV or HIV treatment (e.g. stavudine).18,20 An association with HIV was also noted for psychosis and hypothyroidism (suspected drugs not indicated).18 In contrast, no association was found with 17/18 reported ADR statistically tested and 21/21 ADR statistically tested in two studies.15,39 In one study that focused on peripheral neuropathy, risk was differentiated by incident or prevalent ADR at the start of drug-resistant TB treatment. There was no association with HIV for incident peripheral neuropathy, but prevalent peripheral neuropathy was much more likely for patients who were HIV infected and the risk was increased for those with prolonged prior exposure to stavudine.18 Disaggregation of ototoxicity by HIV status was available for four studies;15,22,36,37 the pooled relative risk (RR) by HIV infection across these studies was not statistically significant (RR: 1.17, 95% CI: 0.93–1.47).

Discussion

Many of the drugs currently used for drug-resistant TB treatment have not undergone robust clinical trials and optimal dosage and side effects are poorly described. This is exacerbated for HIV-infected patients where HIV and ART interactions have not been thoroughly investigated, resulting in inadequate evidence as to the impact of these treatments in the context of high prevalence of HIV coinfection. To understand the prevalence of ADR associated with drug-resistant TB treatment, we searched for studies reporting on ADR during drug-resistant TB treatment where at least 20% of the patients were known to be infected with HIV. Data were extracted...
from 24 studies for the systematic review, but quantitative meta-analysis was limited by inconsistent definitions and reporting categories. No randomized controlled trials with at least 20% of the patient population being HIV infected were identified; this clearly creates a gap in knowledge. Of the 24 studies, 10 counted the patients who experienced at least one ADR and could be included in the main meta-analysis (n = 2776 of whom there were n = 1943 HIV infected); for these studies the pooled proportion of patients experiencing an ADR was 83% (95% CI: 82%–84%).

The 83% experiencing at least one ADR is significantly higher than a previous systematic review and meta-analysis that did not focus on high-burden HIV settings, where 57% of included patients experienced at least one type of ADR, including mild to severe events. HIV could increase the number of ADR due to overlapping toxicities from treatment, but also because of poor clinical condition and advanced disease at presentation, including low CD4 count and low BMI. Although the observational studies reviewed here presented a larger cohort of HIV-infected patients on drug-resistant TB treatment, there was limited analysis of why or how HIV-coinfected drug-resistant TB patients may have had a higher number of reported ADR. There was insufficient disaggregation of the data presented in the included studies to estimate a pooled relative risk by HIV status so as to know whether the difference in pooled proportions (83% versus 57%) was due to chance or was statistically significant. Of the studies that tried to look at ADR by HIV status, more than half found that there was no association or increased risk, but the statistical methods used were not adjusted for potential confounders. One study remarked that while HIV-infected patients experienced fewer ADR, they experienced more death; this may be an indication that the competing risk of death for patients not on ART is the reason that they do not (live long enough to) experience ADR. A study published after the search and systematic review found that HIV-infected patients newly on ART are at increased risk of ADR, if the competing risk of early mortality from not being on ART is accounted for in the analysis.

Fewer than 10 of the studies disaggregated reported ADR by severity; among them, the pooled proportion of patients experiencing at least one severe or worse ADR was 24% (95% CI: 21%–27%). While additional reports would have improved the analysis, severity of the ADR does not always correlate with impact on quality of life and adherence: i.e. pain from injections and nausea from ethionamide although both considered to be ‘mild’ in severity are likely to have a disproportionately large impact on adherence and loss from care due to the significant impact on the patient’s quality of life.

Meta-analysis was limited by non-standard definitions of ADR, severity of ADR and outcomes of the ADR. For example, sometimes the number of patients was reported and in other cases the number of events. Prospective studies sometimes indicated a standard definition of ADR that was defined in advance, such as those required for clinical trials. However, in addition to the potential biases of observational cohorts, few of the studies were prospectively or explicitly designed to report on ADR. Thus, within patient records, ADR that were more severe or more frequent or more surprising may have been more likely to be recorded by the clinician. Within observational reporting, again, those ADR that seemed more interesting may have been more likely to have been included in the write up of the cohort. As noted in many of the studies, ADR that led to a treatment change or a serious outcome (e.g. hospitalization or death) are documented more commonly than those that the patient complains of but did not affect treatment outcome (e.g. headaches, gastrointestinal complaints). And finally, in choosing whether to publish, again there might have been bias. The retrieval and review of studies that summarized only ADR from one particular drug (e.g. clofazimine) or only a specific type of ADR (e.g. hypothyroidism, ototoxicity and peripheral neuropathy) or only those that were serious or severe are examples of how the publication bias potentially affected the availability of evidence related to the prevalence of ADR during drug-resistant TB treatment. In 2016, the WHO recommended a shorter 9 to 12 month regimen for patients who are unlikely to have second-line drug resistance, despite indicating ‘very low certainty in the evidence’, anticipating that reduced exposure time would reduce the burden of ADR. Studies of the shorter regimen were excluded from the meta-analysis and the comparable burden of ADR for the short-course treatment was not evaluated.

Given the high toxicity associated with drug-resistant TB, new drugs will be needed to replace the currently recommended regimens. New drug classes such as those represented by bedaquiline and delamanid, the first new anti-TB drugs approved in 40 years, offer promise for a well-tolerated, injection-free, effective drug-resistant TB regimen. Bedaquiline and delamanid use is recommended where there is either resistance or toxicity to older treatment. Current research priorities include trials of new regimens (rather than adding new drugs to old regimens) where the intention is to both shorten exposure time and to replace the injectables (e.g. kanamycin, amikacin and capreomycin) and all its associated higher risks of ADR. However, it is crucial that these trials include those who are infected with HIV. There is a clear imperative for programmes and countries to develop and implement robust pharmacovigilance systems with standardized reporting at minimum of the number of patients affected, the number of events experienced, the severity of events and the suspected causative agent to allow for meta-analysis and review, particularly as new drugs are rapidly introduced into patient care.

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Supplementary data
Tables S1–S3 and Figure S1 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).
References


