Long-term Risk of Pneumocystosis after Earlier Discontinuation of Prophylaxis among HIV-infected Patients Receiving Highly Active Antiretroviral Therapy

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Abstract

Background  Long-term risk of pneumocystosis after discontinuation of primary or secondary prophylaxis among HIV-infected patients before CD4 counts increase to $\geq 200$ cells/$\mu$L after receiving highly active antiretroviral therapy (HAART) is rarely investigated.

Methods  Between 1 April, 1997 and 30 September, 2007, 660 HIV-infected patients with baseline CD4 counts $<200$ cells/$\mu$L were enrolled in a prospective observational study to assess the incidence rates of pneumocystosis when primary or secondary prophylaxis for pneumocystosis was discontinued before CD4 counts increased to $\geq 200$ cells/$\mu$L after HAART.

Results  Of 521 patients who did not initiate prophylaxis ($n=165$) or discontinued primary or secondary prophylaxis for pneumocystosis before CD4 counts increased to $\geq 200$ cells/$\mu$L ($n=356$) after HAART, 21 cases of pneumocystosis developed after a total observation duration of 1767 persons-years [PY], with an incidence rate of 1.19 per 100 PY (95% confidence interval [CI], 0.77, 1.82). Of 139 patients who continued primary or secondary prophylaxis until CD4 counts increased to $\geq 200$ cells/$\mu$L after HAART, 3 cases of pneumocystosis developed after a total observation duration of 444 PY, with an incidence rate of 0.68 per 100 PY (95% CI, 0.22, 2.10). Compared with the latter group of patients, the risk ratio of developing...
pneumocystosis and all-cause bacterial infections for the former group after earlier discontinuation of prophylaxis was 1.75 (95% CI, 0.5238, 5.886) and 1.58 (95% CI, 0.9859, 2.533), respectively.

**Conclusions** Long-term risk of pneumocystosis was low among patients who discontinued primary or secondary prophylaxis before CD4 increased to $\geq 200$ cells/µL after receipt of HAART with favorable immunological responses.
Background

With the widespread use of highly active antiretroviral therapy (HAART) after 1996, HIV-related mortality and the risks of several major opportunistic infections, such as *Pneumocystis jirovecii* pneumonia (formerly *P. carinii* pneumonia), disseminated *Mycobacterium avium* complex infection, and cytomegalovirus diseases, have significantly declined in patients receiving HAART [1-3]. For example, an incidence rate of 20 cases of pneumocystosis per 100 person-months was reported in the pre-HAART era [4], which decreased to 1.2 cases per 100 person-years (100 PY) of follow-up in the era of antimicrobial prophylaxis for pneumocystosis and HAART [5]. In the HAART era, the majority of cases of pneumocystosis occur in patients who are unaware of their HIV infection or delay in seeking HIV care, or in those with advanced immunosuppression (CD4+ counts <100 cells/µL) who have limited access to HAART and related HIV care [6, 7].

In the guidelines recommended by the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the HIV Medicine Association of the Infectious Diseases Society of America (HIVMA/IDSA) [8] HIV-infected patients should receive trimethoprim-sulfamethoxazole (TMP-SMX) as primary prophylaxis for pneumocystosis if they have a CD4 count of <200 cells/µL. Primary prophylaxis for pneumocystosis can be
discontinued in HIV-infected patients who respond favorably to HAART with an increase in CD4 counts to >200 cells/µL for >3 months. For those who develop pneumocystosis, secondary prophylaxis can be discontinued when their CD4 counts increase from <200 cells/µL to ≥200 cells/µL for more than 3 months as a result of HAART. Findings of several observational studies and clinical trials suggest that the risk of pneumocystosis is low when primary or secondary prophylaxis is discontinued after CD4 count increases to ≥200 cells/µL. In a meta-analysis of 14 published studies, the incidence rate of pneumocystosis is estimated 0.24 per 100 PY and 0.20 per 100 PY in patients discontinued primary and secondary prophylaxis, respectively, who had CD4 count of >200 cells/µL[9].

Prophylaxis or treatment with TMP-SMX is not without problem, however. Skin rashes and fever are the most common adverse effects of TMP-SMX in HIV-infected patients in addition to neutropenia, gastrointestinal intolerance or Stevens-Johnson syndrome [10]. Due to adverse effects of TMP-SMX and limited availability of the alternative agents for prophylaxis, such as primaquine, dapsone, atovaquone, and pentamidine, a certain proportion of the patients that are in need of primary or secondary prophylaxis according to the guidelines may have to discontinue prophylaxis before their CD4 counts
increase to $\geq 200$ cells/$\mu$L. However, studies to assess the safety of earlier discontinuation of pneumocystosis before the CD4 counts increase to $\geq 200$ cells/$\mu$L have not been performed until recently when Jonathan and colleagues followed 19 HIV-infected patients with a median of CD4 count of 120 cells/$\mu$L who discontinued secondary prophylaxis without relapse after an observation duration for 21 months [11]. Though limited by a small sample size and a short observation duration, this study suggests that discontinuation of prophylaxis for pneumocystosis may be safe in selected patients who continue to receive HAART despite of low CD4 counts.

In this study, we aimed to assess the long-term risk of pneumocystosis among HIV-infected patients with baseline CD4 counts of $<200$ cells/$\mu$L who discontinued primary or secondary prophylaxis before their CD4 counts increased to $\geq 200$ cells/$\mu$L after receipt of HAART.
Methods

Study population

Between 1 April, 1997 and 30 September, 2007, consecutive HIV-infected patients who sought HIV care at the National Taiwan University Hospital were enrolled in a prospective observational study to assess the impact of HAART on the incidences of AIDS-defining opportunistic illnesses. The study protocol has been described before [12, 13]. In brief, a standardized case record form was used to record patient characteristics, baseline and sequential CD4 counts and plasma HIV RNA load (PVL), antimicrobial prophylaxis or treatment, antiretroviral therapy, occurrence of AIDS-defining opportunistic illnesses at enrollment and during follow-up, pneumonia or other bacterial infections and parasitic infections.

To assess the impact of HAART on the incidence rate of pneumocystosis, we identified patients who had baseline CD4 counts of <200 cells/µL and had been followed up for more than 3 months. Patients who were lost to follow-up or died within 3 months of enrollment were excluded (Figure 1).

Prophylaxis for pneumocystosis and HAART

In Taiwan, HIV-infected patients are provided free-of-charge access to HIV
care, including HAART which was introduced on 1 April, 1997, at several
designated hospitals around Taiwan. HAART consisted of two nucleoside
reverse-transcriptase inhibitors (RTI) plus non-nucleoside RTI or protease
inhibitors (PI); or triple nucleoside RTI. Treatment and prophylaxis for
pneumocystosis included TMP-SMX (400/80 mg). For those patients who were
unable to tolerate TMP-SMX, prophylaxis or treatment was replaced with
clindamycin plus primaquine [14]. Atovaquone or dapsone was not available
for pneumocystosis prophylaxis in Taiwan, while pentamidine was available
only before 1997. The decision of discontinuation of prophylaxis or switch to
clindamycin plus primaquine for pneumocystosis in the face of adverse effects
of TMP-SMX was at the discretion of treating physicians.

**Follow-up and end points**

After initiation of HAART, patients received follow-up at an interval of 1 to
3 months. Each visit included a medical history taking, a general physical
examination, and laboratory tests including complete blood count with
differential count and blood biochemistry. CD4 count and PVL were
determined before and 1 month after HAART and every 3-4 months thereafter.
A chest radiograph and microbiological investigations were performed when
patients presented with respiratory symptoms or a history of prolonged fevers
or wasting.

Pneumocystosis was confirmed when cytology or histopathology of respiratory specimens disclosed cysts or trophozoites by special stains; pneumocystosis was considered presumptive if the patients presented with typical symptoms (resting or exertional dyspnea, nonproductive cough, hypoxemia, and elevated lactate dehydrogenase levels), plus radiographic manifestations of interstitial pneumonitis who responded to any of the standard recommended treatments for pneumocystosis.

Other than pneumocystosis, we also assessed the incidence of bacterial infection and parasite infestation after discontinuation of primary or secondary prophylaxis. A diagnosis of bacterial infection was made on microscopy and microbiology of relevant clinical specimens and a compatible clinical history that included an acute onset of symptoms, with a response to anti-bacterials that have no known activity against pneumocystosis. Parasitic infestations were defined as amebiasis, giardiasis, cryptosporidiosis, isoporiasis, cyclosporiasis, and toxoplasma encephalitis with compatible clinical symptoms, and a response to specific anti/protozoals.

**Statistical Analysis**

The observation duration for occurrence of pneumocystosis was
estimated from the date of discontinuation of primary or secondary prophylaxis until the date of diagnosis of pneumocystosis, loss to follow-up at this hospital, death, or the end of the study, whichever occurred first. The end date of this observational study was 31 December, 2007.

All statistical analyses were performed using a statistical software program (SAS version 8.1; SAS Institute Inc, Cary, NC). Categorical variables were expressed as proportions and compared using $\chi^2$ by Fisher exact test (2-tailed). The incidence rate for each group was calculated as the number of cases of pneumocystosis, bacterial infection or parasitic infestations per 100 PY of observation. Exact 95% confidence intervals (95% CI) for incidence rates were calculated on the basis of the Poisson distribution.
Results

Patient characteristics

Between April 1997 and September 2007, 660 patients fulfilled the inclusion criteria (Figure 1): 165 patients who had baseline CD4 counts of \(<200 \text{ cells/µL}\) were not prescribed with primary prophylaxis for pneumocystosis; and 279 and 216 patients received primary and secondary prophylaxis, respectively. Their demographic and clinical characteristics at enrollment are shown in Table 1. Most patients were men, and the risk factor of HIV transmission was predominantly male homosexual contact.

Of the 279 patients who received primary prophylaxis, 211 (75.6%) discontinued prophylaxis before CD4 increased to \(\geq 200 \text{ cells/µL}\), and 68 (24.4%) continued prophylaxis until CD4 increased to \(\geq 200 \text{ cells/µL}\). Compared with the latter group of patients, the former group of patients were older (mean age, 35 vs 39 years; \(P=0.03\)) and had a lower baseline CD4 count (mean, 65 vs. 38 cells/µL; \(P<0.001\)) (Table 1), while both groups of patients had similar baseline PVL (mean, 5.62 vs 5.53 \(\log_{10}\) copies/ml; \(P=0.13\)).

Of the 216 patients who received secondary prophylaxis, 145 (67.1%) discontinued prophylaxis before CD4 increased to \(\geq 200 \text{ cells/µL}\), and 71 (32.9%) continued prophylaxis till CD4 increased to \(\geq 200 \text{ cells/µL}\) (Table 1).
Compared with the latter group of patients, the former group of patients were older (35 vs. 38.6 years; \( P=0.006 \)), had a lower baseline CD4 count (50 vs. 25 cells/µL; \( P<0.001 \)) and had a higher baseline PVL (5.60 vs 5.68 log\(_{10}\) copies/ml; \( P=0.04 \)) (Table 1).

Of the 165 patients who did not receive primary or secondary prophylaxis, their baseline CD4 count was 125 cells/µL, and PVL was 5.40 log\(_{10}\) copies/ml (Table 1).

**Trends of CD4 cell counts after HAART**

Of the 211 patients who discontinued primary prophylaxis before CD4 counts increased to \( \geq 200 \) cells/µL received primary prophylaxis for a mean duration of 5.7 months (standard deviation [SD], 8.1). After discontinuation of primary prophylaxis, their CD4 counts continued to increase with time while they continued HAART (Figure 2a) and the latest CD4 count was 300 cells/µL (SD, 228) after a follow-up duration of 42.8 months (SD, 31.6).

Of the 145 patients who discontinued secondary prophylaxis before CD4 counts increased to \( \geq 200 \) cells/µL received secondary prophylaxis for a mean duration of 6 months (SD, 8.9). After discontinuation of secondary prophylaxis, their CD4 counts continued to increase with time while they continued HAART.
(Figure 2b) and the latest mean CD4 count was 343 cells/µL (SD, 230) after follow-up for 46.8 months (SD, 31.7).

Among the 165 patients who did not receive any prophylaxis, their latest mean CD4 count was 358 cells/µL (SD, 242) after follow-up for 35.9 months (SD, 28.9) while they continued HAART (Figure 2c).

**Incidence of events during Follow-up**

The crude incidence of adverse effects of primary prophylaxis with TMP-SMX was estimated 23.3%, which included skin rashes (13.3%), leucopenia (6.8%), gastrointestinal intolerance (2.9%), and Stevens-Johnson syndrome (0.4%). Of the 211 patients who discontinued primary prophylaxis before CD4 count increased to ≥200 cells/µL, 11 patients was subsequently diagnosed as having pneumocystosis, with an incidence rate of 1.52 per 100 PY (95% CI, 0.84 to 2.74) (Table 2). These 11 episodes of presumptive diagnosis of pneumocystosis occurred in patients with a median CD4 count of 33 cells/µL (range, 3-182) after a median observation of 13.7 months (range, 2.23-92.4) in the absence of primary prophylaxis. Those episodes occurred in patients with frequent losses to follow-up for more than 1 year or poor compliance with HAART and virologic failure (9 patients) and intolerance (2).

Of 68 patients who discontinued primary prophylaxis until CD4 counts
increased to $\geq 200$ cells/µL, 1 patient was diagnosed with pneumocystosis, with an incidence rate of 0.43 per 100 PY (95% CI, 0.06 to 3.04). There was no statistically significantly difference between the two incidence rates ($P=0.20$). In the meantime, 62 episodes of bacterial infections were diagnosed in patients who discontinued primary prophylaxis before CD4 counts increased to more than 200 cells/µL, yielding an incidence rate of 8.59 per 100 PY (95% CI, 6.68 to 11.0), while 13 episodes were diagnosed in the patients who discontinued primary prophylaxis after CD4 counts increased to $\geq 200$ cells/µL, yielding an incidence rate of 5.56 per 100 PY (95% CI, 3.23 to 9.59). There was no statistically significantly difference between the two incidence rates of bacterial infections ($P=0.17$). The types of bacterial infections of the former group included skin and soft tissue infection (37 cases), community-acquired pneumonia (9), urinary tract infection (7) and bacteremia due to methicillin-resistant *Staphylococcus aureus*, non-tuberculous mycobacteria or non-typhoid *Salmonella* (9).

Two episodes of parasitic infection (toxoplasmosis), with an incidence rate of 0.28 per 100 PY (95% CI, 0.07 to 1.11), occurred in the patients who had discontinued primary prophylaxis until a CD4 count increased to $\geq 200$ cells/µL.
Forty-seven patients (21.8%) developed adverse effects that prompted discontinuation of secondary prophylaxis; those adverse effects included skin rashes (17.6%), gastrointestinal intolerance (2.3%) and leucopenia (1.9%). Of the 145 patients who discontinued secondary prophylaxis before CD4 counts increased to ≥200 cells/µL, 7 were diagnosed with pneumocystosis, with an incidence rate of 1.26 per 100 PY (95% CI, 0.60 to 2.23) (Table 2). These 7 cases of presumptive pneumocystosis occurred in patients with a median CD4 count of 4 cells/µL (range, 1-50) after a median observation of 22.9 months later (range, 8.9-69.3) in the absence of secondary prophylaxis. The episodes occurred in patients who had poor compliance with HAART or virologic failure. The incidence rate of pneumocystosis was 0.95 per 100 PY (95% CI, 0.24 to 3.80) in 71 patients who discontinued secondary prophylaxis until CD4 counts increased to ≥200 cells/µL. There was no statistically significantly difference between the two incidence rates (P=0.73). In total, 29 episodes of bacterial infections were diagnosed in patients who discontinued secondary prophylaxis before CD4 counts increased to ≥200 cells/µL, yielding an incidence rate of 5.2 per 100 PY (95% CI, 3.61 to 7.49); and 7 episodes were diagnosed in patients who discontinued secondary prophylaxis after CD4 counts increased to ≥200 cells/µL, yielding an incidence rate of 3.33 per 100 PY (95% CI, 1.59
to 6.99). The types of bacterial infections in the former group included skin and soft tissue infection (17 cases), community-acquired pneumonia (5), urinary tract infection (2) and bacteremia due to *S. aureus* or non-typhoid *Salmonella* (5). There was no statistically significantly difference between the two incidence rates of bacterial infections (*P*=0.30). Three episodes of parasitic infections (two amebiasis and one giardiasis), yielding an incidence rate of 0.54 per 100 PY (95% CI, 0.17 to 1.67), occurred in patients who discontinued secondary prophylaxis until CD4 counts increased to $\geq 200$ cells/µL.

The incidence rate of pneumocystosis in 165 patients who had baseline CD4 counts of $<200$ cells/µL and did not receive either primary or secondary prophylaxis for pneumocystosis was 0.62 per 100 PY (95% CI, 0.20 to 1.91) (Table 2). Thirty-five episodes of bacterial infections were diagnosed, yielding an incidence rate of 7.19 per 100 PY (95% CI, 5.16 to 10.0) and three episodes of parasitic infections (2 amebiasis and 1 toxoplasmosis), with an incidence of 0.62 per 100 PY (95% CI, 0.20 to 1.91). The types of bacterial infections included skin and soft tissue infection (19 cases), community-acquired pneumonia (5), urinary tract infection (4) and bacteremia due to *Escherichia coli* or non-typhoid *Salmonella* (7).

When patients who did not initiate prophylaxis or discontinued primary or
secondary prophylaxis for pneumocystosis before CD4 counts increased to \( \geq 200 \) cells/\( \mu L \) after HAART were analyzed together, 21 cases of pneumocystosis developed after a total observation duration of 1767 persons-years [PY], with an incidence rate of 1.19 per 100 PY (95% confidence interval [CI], 0.77, 1.82). Of 139 patients who continued primary or secondary prophylaxis until CD4 counts increased to \( \geq 200 \) cells/\( \mu L \) after HAART, 3 cases of pneumocystosis developed after a total observation duration of 444 PY, with an incidence rate of 0.68 per 100 PY (95% CI, 0.22, 2.10). Compared with the latter group of patients, the unadjusted risk ratio of developing pneumocystosis and all-cause bacterial infections for the former group after earlier discontinuation of prophylaxis was 1.75 (95% CI, 0.5238, 5.886) and 1.58 (95% CI, 0.9859, 2.533), respectively.
**Discussion**

In this prospective observational study, we found that, compared with incidence rate of the patients who continued primary or secondary prophylaxis until CD4 counts increased to \( \geq 200 \text{ cells/µL} \) after HAART, the incidence rate of pneumocystosis was similarly low among HIV patients who did not initiate prophylaxis or discontinued primary or secondary prophylaxis when CD4 counts remained \(<200 \text{ cells/µL} \) : 0.68 per 100 PY (95% CI, 0.22, 2.10) vs. 1.19 per 100 PY (95% confidence interval [CI], 0.77, 1.82) (unadjusted risk ratio, 1.75; 95% CI, 0.52, 5.88).

The incidence rates of pneumocystosis following discontinuation of primary and secondary prophylaxis among HIV-infected patients when their CD4 counts increased to \( \geq 200 \text{ cells/µL} \) after receiving HAART in published studies ranged from 0 to 2.27 cases per 100 PY of follow-up, depending on the types of study design and observation duration [3, 11, 15-25] (Table 3). Our observational study conducted in a clinical setting where options of antimicrobial prophylaxis are limited showed an overall rate of 1.19 cases per 100 PY (95% CI, 0.77, 1.82) after earlier discontinuation of primary or secondary prophylaxis, which is within the range of reported incidence rates of case series and cohort studies (Table 3).

Discontinuation of prophylaxis before CD4 counts increase to \( \geq 200 \)
cells/µL after HAART has been performed in some selected patients in published observational studies [11, 15, 17]. In one study, primary or secondary prophylaxis was discontinued when CD4 count was <200 cells/µL in 98 patients who received HAART without occurrence of pneumocystosis [15]. In a recent study by Jonathan and colleagues [11], no recurrence of pneumocystosis was demonstrated in 19 patients who had a median CD4 count of 120 cells/µL and achieved sustained HIV viral suppression after prophylaxis for pneumocystosis was discontinued during the mean follow-up duration of 13.7 months. Therefore, earlier discontinuation of prophylaxis appears to be safe in selected patients who have a favorable immunologic or virologic response to HAART. Our study further provides the safety data of earlier discontinuation of primary and secondary prophylaxis for 3 to 4 years of follow-up. As shown in figures 2a, 2b and 2c, CD4 count will be on the increasing trends after HAART if the HIV-infected patients adhere to HAART with favorable virologic responses.

Earlier discontinuation of TMP-SMX or other alternatives in the patients with increasing CD4 counts may reduce pill burden, risk for adverse effects of TMP-SMX that was noted in one fourth of our patients, and risk for emergence of drug-resistant bacteria [26-28]. However, the benefit should also be
balanced against risk because use of TMP-SMX is associated with decreased risk for bacterial infections [29, 30]. In our study, the incidence rate of all-cause bacterial infection was estimated 5.2-8.59 per 100 PY of follow-up after discontinuation of prophylaxis for pneumocystosis, which appears to be similar to those of previous studies (Table 3).

Our findings that most of the cases of pneumocystosis occurred in patients who did not have good adherence to HAART and HIV care should alert clinicians and patients with respect to the risk if decision of earlier discontinuation of prophylaxis has to be made in the face of adverse effects of antibacterial agents. For those who have to discontinue primary or secondary prophylaxis due to intolerance or adverse effects, adherence to HAART can not be overemphasized. Reinstitution of prophylaxis should be considered once immunologic failure occurs after virologic failure to HAART due to poor compliance and emergence of HIV that is antiretroviral-resistant.

There are several limitations of our study and interpretation of our study should be cautious. First, this is not a clinical trial to compare the risk for pneumocystosis between patients who discontinue primary or secondary prophylaxis when their CD4 counts remain <200 cells/µL and those who discontinue prophylaxis when their CD4 counts increase to ≥200 cells/µL. The
decision of discontinuation of prophylaxis was made by treating physicians based on individualized assessment, which may be affected by uncontrolled factors. Second, the diagnosis of pneumocystosis was based on clinical suspicion and an appropriate response to any of the recommended standard treatments and the absence of evidence of bacterial pneumonia. All of our diagnoses were presumptive, not definitive. Third, the results of this study of early discontinuation of pneumocystosis prophylaxis may not be generalizable to the patients with virologic and immunological failure or patients with limited access to HAART and HIV care. Fourth, the benefits of TMP-SMX in resource-limited settings are multiple in addition to its low cost, and continuation of TMP-SMX can protect patients from several bacterial or parasitic infections [31-33]. In such settings, benefits of continuation of TMP-SMX may still outweigh the risks associated with earlier discontinuation of TMP-SMX after programs of antiretroviral therapy is increasingly implemented in these regions.

In conclusions, we found that the long-term risk of pneumocystosis was low among HIV-infected patients who discontinued primary and secondary prophylaxis before CD4 cell counts increased to \( \geq 200 \) cells/\( \mu l \) while they continued to receive HAART.
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Kumarasamy N, Vallabhaneni S, Cecelia AJ, Mayer KH, Solomon S, Carpenter CC, Flanigan TP. **Safe discontinuation of primary pneumocystis prophylaxis in Southern Indian HIV-infected patients on highly active antiretroviral therapy.**

Competing interests

Non-financial competing interests
Figure 1. Study population of discontinuation of primary and secondary prophylaxis in HIV-infected patients between April 1997 and September 2007

Between April 1997 and September 2007, 1674 HIV infected patients

- 847 patients with CD4 ≥ 200 µL
- 18 patients, no CD4 data
- 12 patients, missing of medical record

797 patients with CD4<200 µL

- 137 patients lost to follow-up or death before discontinuation of prophylaxis

279 patients received primary prophylaxis

216 patients received secondary prophylaxis

165 patients without PCP prophylaxis

211 patients discontinued prophylaxis before CD4 ≥ 200

145 patients discontinued prophylaxis before CD4 ≥ 200

11 patients with new PCP

7 patients with recurrent PCP

3 patients with new PCP
Figure 2a. Evolution of CD4 cell counts in 211 patients who received highly active antiretroviral therapy and primary prophylaxis for *Pneumocystis jirovecii* pneumonia, the latter subsequently discontinued before CD4 cell counts increased to ≥200 cells/µL.
Figure 2b. Evolution of CD4 cell counts in 145 patients who received highly active antiretroviral therapy and secondary prophylaxis for *Pneumocystis jirovecii* pneumonia, the latter subsequently discontinued before CD4 cell counts increased to \( \geq 200 \) cells/µL.
Figure 2c. Evolution of CD4 cell counts in 165 patients who only receive highly active antiretroviral therapy, but not any prophylaxis for *Pneumocystis jirovecii* pneumonia.
Additional files provided with this submission:

Additional file 1: bmc-table.doc, 159K
http://www.biomedcentral.com/imedia/1993154782885828/supp1.doc