Optimal timing for discontinuation of Pneumocystis jiroveci pneumonia prophylaxis in adult patients on highly active antiretroviral therapy (HAART) for HIV infection.

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Background: *Pneumocystis jiroveci* pneumonia (PJP) is one of the most common opportunistic infections in HIV-infected individuals. Although the introduction of Highly Active Antiretroviral Therapy (HAART) and PJP prophylaxis has greatly reduced the incidence of PJP in HIV-infected individuals, PJP is still extremely common in HIV-infected patients not yet on HAART. Recent guidelines advise the safe discontinuation of PJP prophylaxis in HIV patients on HAART with a stable increase in CD4 count to above 200 cells/mm^3 for at least 3 months. Discontinuation of PJP prophylaxis would reduce HIV patients' pill burden as well as the overall cost of HIV management. The potential for drug toxicity, harmful drug interactions and the development of drug resistant pathogens would also be reduced. However, reports of PJP occurring in HIV patients with CD4 counts above 200cells/mm^3 question the safety of this intervention.

Objectives: To assess the impact of discontinuation of *Pneumocystis jiroveci* prophylaxis on the morbidity and mortality due to *Pneumocystis jiroveci* pneumonia in HIV-infected patients who show a stable rise in CD4 counts to >200cells/mm^{3}for three months or more following initiation of HAART.

Methods: We searched for relevant studies in the following databases: MEDLINE (from 1995 to 7 December 2011), EMBASE (from 1995 to 10 February 2012), CENTRAL (The Cochrane Library 2011, Issue 4 of 4), CINAHL (from 1995 to 3 December 2011), LILACS (from 1995 to 3 December 2011), WHO Global Health Library, AEGIS database of HIV/AIDS conferences, NLM Gateway, individual conference web sites and prospective trials registers. We contacted experts in the field and scanned references of relevant studies and review articles for further trials. No language restrictions were used.

Results: Four RCTs met the inclusion criteria. No cases of PJP or *Toxoplasmosis gondii* infection were reported in either of the two RCTs investigating discontinuation of primary prophylaxis in HIV-infected individuals on HAART with CD4 counts above 200 cells/mm^3 (Mussini 2000; Lopez 2001). A meta-analysis of the two trials showed no statistically significant difference in the rates of occurrence of other HIV-related events between the two treatment groups (N= 1182; RR: 0.83; 95% CI: 0.25 to 2.69; heterogeneity: Chi^2= 0.02, df=1, (p= 0.90); I^2= 0%). Furthermore, a meta-analysis of the two RCTs showed no statistically significant difference in the rates of all-cause mortality among patients that discontinued primary prophylaxis and those that continued the primary prophylaxis (N=1182; RR: 1.32; 95% CI: 0.30 to 5.86; heterogeneity: Chi^2= 0.06, df=1, (p= 0.80); I^2= 0%). There was also no significant difference in adverse events in participants who continued primary prophylaxis compared to participants who discontinued primary prophylaxis (1 study, N= 474; RR: 0.86; 95% CI: 0.51 to 1.47). Two studies investigated the safety of discontinuing secondary PJP prophylaxis in HIV-infected individuals on HAART with CD4 counts above 200 cells/mm^3. No cases of PJP were reported in Lopez 2001. In Mussini 2003, two cases of PJP were reported in the discontinuation arm and no cases of PJP were reported in continuation arm. This difference in the number of reported cases of PJP was not statistically significant (N=146; RR: 4.49, 95% CI: 0.22 to 91.87). No deaths, cases of Toxoplasmosis gondii infection, or other HIV-related events were reported by the two studies. Lopez 2001 reported no statistically significant difference in the rate of adverse events between the two treatment arms. One participant in each treatment group had an episode of bacterial pneumonia (N=113; RR: 0.88; 95%CI: 0.06 to 13.78). Campbell 2012, a cluster RCT conducted in Africa, showed a non-statistically significant reduction in the risk of death (0.2% versus 0.6%; p= 0.63) in patients who discontinued PJP prophylaxis compared to those who continued prophylaxis. They also reported an increase in the risk of adverse events in the patients who discontinued PJP prophylaxis compared to those who continued prophylaxis. Though the increase in the risk of hospitalisations (2.9% versus 1.3%; p=0.19) was not statistically significant, there was a statistically significant increase in the risk of malaria [RR=2.7, (95% CI; 2.1 to 3.5; p = <0.001)], diarrhoea [RR= 1.8 (95%CI; 1.3 to 2.4; p= < 0.001) and respiratory tract infections (154 (40%) versus 133 (29%); p=0.002).

Authors' conclusions: These studies provide moderate to low quality evidence that there was no statistically significant difference in the risk of acquiring PJP, toxoplasmosis, death and occurrence of HIV related events between the patients who discontinued PJP prophylaxis and those who continued PJP prophylaxis. However, discontinuation of PJP prophylaxis was associated with statistically significant increases in the risk of malaria, diarrhoea and respiratory infections in one study. Based on the available evidence, the decision to discontinue PJP prophylaxis in the clinical setting should be patient specific taking into account the available health facilities and disease profile of the region