Table 4b. TIV in individuals with HIV/AIDS

Is inactivated influenza vaccine versus placebo effective to prevent influenza infection in individuals living with HIV/AIDS?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		2 RCT[1, 2, 3]	4
	Factors decreasing confidence	Limitation in study design	Serious[4]	-1
		Inconsistency	Very serious[5]	-2
		Indirectness	None serious[6]	0
		Imprecision	Serious[7]	-1
		Publication bias	None serious[8]	0
	Factors increasing confidence	Strength of association/ large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic /mitigated bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**1** (numerical rating 0 but value cannot be <1)
Summary of Findings	**Statement on quality of evidence**			Our confidence in the estimate of effect of influenza vaccination of individuals living with HIV/AIDS on influenza is low.
	Conclusion			In HIV-infected individuals, influenza vaccine (TIV) was **significantly more efficacious than placebo and showed an efficacy of** 75.5% (95% CI: 9.2 to 95.6).[9, 10] No significant difference was observed between vaccine and placebo recipients for ILI or physician attended acute respiratory infection illness.[11]

NOTES

[1] The first RCT identified (Madhi et al. 2011) analyses the efficacy of TIV vaccination versus placebo against influenza illness in 506 HIV-infected adults with CD4+ counts of >100 cells per microlitre in South Africa. Influenza infection was confirmed by shell vial culture or through real-time RT-PCR. Among the secondary outcomes assessed were ILI and acute respiratory illness. 189 of the study participants were co-enrolled for a nested immunogenicity study.
The second RCT by Tasker et al. 1999 studied 102 HIV-positive adult individuals. 55 received influenza vaccine and 47 placebo. Efficacy measures obtained from this trial (93%) are summarized in note 10.

[2] There were two meta-analysis available (Anema et al. 2008, Atashili et al. 2006) that included studies of different design and quality. Anema et al. 2008 calculated a pooled relative risk reduction, i.e. effectiveness of 66% (relative risk 0.34; 95% CI: 0.18 to 0.64) for influenza vaccines in preventing symptomatic influenza in HIV-positive individuals. The estimate is based on one RCT that assessed confirmed influenza (Tasker et al. 1999, included in grading, see note 1) and two prospective cohort studies (Ranieri et al. 2005, Yamanaka et al. 2005). It was mentioned that considering the RCT only, a far more conservative estimate of relative risk reduction has been achieved (41%; 95% CI: 2 to 55%).
The second meta-analysis by Atashili et al. (2006) included the same studies as the first analysis by Anema et al. (2008) as well as an additional case-control study by Fine et al. 2001. Vaccine effectiveness extracted from the four studies ranged from 27-78% and an overall significant reduction in occurrence of influenza

cases achieved by influenza vaccination was reported (Atashili et al. 2006). The estimates obtained from the two meta- analyses are subject to bias resulting from major limitations such as pooling of different study designs (case-control study with prospective studies in Atashili et al. 2006 and observational studies with RCTs in Atashili et al. 2006 and Anema et al. 2008). In addition, Atashili et al. 2006 did not present a detailed search concept.
Across the observational studies available (Fine et al. 2001, Ranieri et al. 2005, Yamanaka et al. 2005), comparison groups and outcomes used vary greatly. Yamanaka et al. 2005 compare HIV-positive TIV recipients with HIV-positive unvaccinated individuals whereas Ranieri et al. 2005 compare HIV-positive individuals co-vaccinated for pneumonia and influenza with HIV-positive individuals vaccinated for pneumonia. The case-control study/outbreak investigation by Fine et al. 2001 compares vaccinated and unvaccinated HIV-positive individuals in terms of ILI occurrence. Participants of these observational studies were not assigned randomly and no study provided a placebo for the control arm. Due to the availability of RCTs and the methodological drawbacks of the observational studies, they were not included into the grading process.

[3] Immunogenicity and safety of influenza vaccine in HIV-infected individuals was assessed in several trials (e.g. Madhi et al. 2011, Kajaste-Rudnitski et al. 2011). Kajaste-Rudnitski et al. 2011 reports that antibody titres after vaccination with pandemic influenza vaccination were similar in HIV-positive individuals under HAART compared to HIV-negative individuals. Results from the multivariate analysis of this study indicate that HIV-positive individuals were less likely to seroconvert post-vaccination resulting in a higher proportion of individuals that seroconvert in the HIV-negative than in the HIV-positive group. However, differences were suggested to arise from different HAI baseline titres. No factor related to HIV-infection (e.g. CD4+ cell count, HIV-RNA load) influenced the achievement of protective antibody levels post-vaccination. Similarly, Madhi et al. 2011 and Tasker et al. 1999 reported that immunization did not affect CD4+ cell counts and viral load.
An immunogenicity study that was nested into the trial by Madhi et al. 2011 used other comparison groups (HIV-positive TIV-recipients versus HIV-positive placebo recipients for the efficacy assessment, TIV-vaccinated ART-naïve adults versus TIV-vaccinated individuals on stable ART for additional safety and immunogenicity assessment) and found a significant higher seroconversion rate among TIV recipients when compared to placebo as well as a proportionally lower serconversion among ART-naïve compared to ART-stable adults receiving TIV.
Regarding the safety profile of influenza vaccination, no serious adverse event or dropout related to adverse events were reported for HIV-positive individuals by Kajaste-Rudnitski et al. (2011) and there was no significant increase in HIV viraemia compared to baseline. Similarly, no significant differences in solicited adverse events between HIV-positive TIV or placebo recipients were observed in the study by Madhi et al. 2011.

[4] Blinding and randomization was appropriate in the RCTs but reporting overall was not comprehensive. This applies particularly to the inconclusive assessment of loss to follow-up (Tasker et al. 1999). Differences between control and intervention group were not assessed statistically and bias might be introduced by the fact that serum samples were not available for all participants (e.g. 20 out of 39 that reported respiratory illness came for viral respiratory culture in Tasker et al. 1999).

[5] Heterogeneity was very high between the two trials and between the available observational studies (see also note 2) in terms of setting, country, population studied, and comparison group used as well as regarding the median/mean CD4+ cell counts of study participants. A high and significant heterogeneity was also reported from the meta-analyses (Anema et al. 2008, Atashili et al. 2006), which is, however likely to be related to pooling of different study designs.

[6] Drifts from influenza strains included in TIV compared to circulating strains may have impacted on the efficacy measure, but this fact applies to the majority of studies and risk groups evaluated for influenza vaccine efficacy. Therefore, no downgrading was applied here. The change in ART regimens of some study

participants in Tasker et al. 1999 may have rather affected vaccine effects on viral replication and immunogenicity outcomes.

[7] Wide CIs (Madhi et al. 2011) and low attack rates as well as small number of observed events (Tasker et al. 1999). In Madhi et al. 2011, the low attack rates of confirmed influenza among controls and the potential under- enrollment was reported to be partly offset by low loss to follow-up.

[8] Atashili et al. 2006 did an assessment of publication bias but did not find evidence.

[9] Madhi et al. 2011. H1N1 specific efficacy was 73.3% (95% CI: 1.2 to 95.2).

[10] The trial by Tasker et al. reported a 100% effectiveness of influenza vaccine against symptomatic influenza as well as significant differences ($p<0.001$) between placebo and influenza vaccine regarding laboratory-documented influenza infection as confirmed by culture or serologic examination resulting in an efficacy of 93% (95% CI: 69 to 100). The numerical values from this trial are not reported in the grade table since the estimates by Madhi et al. 2011 are reported more conclusively and are in the range of results from other available studies (observational, see note 2).

[11] Madhi et al. 2011, Tasker et al. 1999.

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