Supplementary Table S1: Monitoring strategies

Study	Time to toxic event	Type of AE monitoring		Frequency of AE monitoring	
		Symptom*	Laboratory	Baseline	Routine
Boulle, 2008	Change NVP: 8 weeks EFV: 6 weeks	Unclear	ALT	Yes	Monthly for first 3 months, then every 3 months
Bruck, 2008	Liver enzyme elevation EFV 20 weeks NVP: 16 weeks	No	AST, ALT	Yes	Every 8 weeks
Castlenuovo, 2011	Not stated	No	Full blood count, AST, Creatinine, serum lactate	Not stated	Every 6 months
Elzi, 2010	Not stated	Not stated	Not stated	Not stated	Not stated
Ferradini, 2006	Not stated	Yes	Full blood count, chemistry	Yes	No
Forna, 2007	Not stated	Yes (Medical officer or self-referral)	Full blood count, Creatinine, ALT, AST	Yes	No
Gaytan, 2004	Not stated	Yes	Yes	Yes	Every 4 weeks
George, 2009	Not stated	Not stated	Not stated	Not stated	Not stated
Haddow, 2007	Not stated	Not stated	Not stated	Not stated	Not stated
Ibadova, 2010	Not stated	Not stated	Not stated	Not stated	Not stated
Jena, 2009	Not stated		Hb, TLC, platelets, CD4, ALT, AST	hemogram, liver function test, renal function test, lipidogram, ECG, and chest x-ray	2,6,14 and 24 weeks
Kampire	NS	Yes	Yes	NS	NS
Kalyesubula, 2011	Not stated	No	Full blood count, ALT	Complete blood count and ALT	2, 6, 10 and 14 weeks only ALT
Khalili, 2009	Not stated	No	Full and differential blood counts, ALT, AST, Alk.P, TBR, Creatinine, BUN, triglycerides, total cholesterol, LDL, HDL, blood fasting sugar, lactate, CPK	Yes	Monthly: blood counts 3, 6, 12 months: lipids, fasting blood sugar, liver and renal function, lactate, CPK 2, 4, 8, and 12 weeks if on NVP: liver function
Kumarasamy, 2008a	Not stated	Yes	Hb, liver, and renal function tests	Not stated	Every 3 months or as clinically indicated
Kumarasamy, 2008b	Not stated	Yes	Hb, Creatinine, ALT, AST	Not stated	Not stated
Manfredi, 2006	NVP: 4.2±1.8 months EFV: 7.8±2.6 months	Not stated	ALT, AST	Yes	Not stated
Mankhatitham, 2011	Not stated	No	Full blood count, blood chemistries and AST, ALT, TBR	Yes Liver function tests only	6, 12 and 24 weeks
Messou, 2010	NVP: 4.8 months EFV: 12.8 months	Yes	Creatinine, ALT, AST	Yes Creatinine, ALT, AST	Every 6 months
Modayil, 2010	Not stated	Not stated	Not stated	Not stated	Monthly for newly registered pts; spontaneous reporting for longer term pts

Nunez, 2002	Not stated	Yes	Full blood count, liver (AST, ALT) and kidney function tests, amylase and lipid profile (including cholesterol, triglycerides)	No	Every 3 months
Obiako, 2012	Not stated	No	Blood chemistry and hematology	Yes	Every 12 weeks; visits for complaints
Patel, 2006	Not stated	Yes	ALT	Not stated	Monthly then 3 monthly
Ritchie, 2006	Not stated	Not stated	ALT, AST	Yes	Yes (frequency not stated)
Sanne, 2005	HT: 28 days	No	ALT, AST	Yes	Monthly
Sivadasan, 2009	Rash: 2 weeks	Yes	ALT, AST	Yes	2 weeks, 1 month, then every 3 months
Srirangaraj, 2010	NVP: 77 days EFV: 118 days	No	Full blood count, AST, ALT, TBR, creatinine	Yes (Hb, ALT, TBR, creatinine)	3 monthly
Sulkowski, 2002	NVP: 137 days EFV: 100 days	No	Full blood count, ALT, AST, TBR	Yes	4 weeks, then 3 monthly
Swaminathan, 2011	Not stated	Yes (monthly)	Full blood count, liver function (tests not stated)	[0]Hematological analysis, blood glucose levels, and liver and renal function tests	2 weeks for 8 weeks, then 3 monthly
Tukei, 2012	Not stated	Yes	Full blood count, ALT, AST	Yes	Monthly
van den Berg-Wolf, 2008	Not stated	Yes	ALT, AST	Not stated	1 month, then 4 monthly
Van Leth, 2004	Not stated	No	ALT, AST, TBR	Yes	2, 4, 8, 12, 24, 36 and 48 weeks
Wester, 2010	Treatment modifying toxicity NVP: c. 14 days EFV: c. 40 days	lipodystrophy (every 6 months), peripheral neuropathy (every 2 months)	Chemistry, full blood count, lipid chemistry	Yes	Monthly for 6 months then 2 monthly for 6 months, then 4 monthly
Zhou, 2006	Not stated	Not stated	Not stated	Not stated	Not stated

* [0]Defined as necessary for the laboratory test to be performed (i.e. not routine)
AlkP Alkaline Phosphatase
ALT Alanine transaminase
AST Aspartate aminotransferase
BUN Blood Urea Nitrogen
CPK Creatinine phosphokinase
Hb Haemaglobin
LDL and HDL Low-density and High-density lipoprotein cholesterol
TBR Total Bilirubin
TLC Total leucocyte count

Supplementary Table S2: Risk of bias

Study	Baseline characteristics balanced (details)	Unbiased reporting of outcomes	Loss to follow up <20%	Allocation concealment reported (for RCTs)	Minimal follow up time (may exclude early discontinuations)	Differential follow up by drug	Overall risk of bias
Boulle, 2008	Yes	Yes	Yes	N/A	No	No	Low
Bruck, 2008	No[1]	Yes	Yes	N/A	No	No	Low
Castlenuovo, 2011	--	--	Yes	N/A	No	No	Moderate
Elzi, 2010	--	Yes	Yes	N/A	Yes	No	Low/moderate
Ferradini, 2006	--	Yes	Yes	N/A	Yes	No	Low/moderate
Forna, 2007	--	Yes	--	N/A	No	No	Low
Gaytan, 2004	Yes	Yes	No	--	No	No	Low/moderate
George, 2009	--	No	No	N/A	--	--	Low/moderate
Haddow, 2007	--	Yes	Yes	N/A	No	Yes	Low/moderate
Ibadova, 2010	--	--	--	--	--	--	High
Jena, 2009	--	Yes	Yes	N/A	No	No	Low
Kalyesubula, 2011	--	Yes	Yes	N/A	Yes	Yes	Low/moderate
Khalili, 2009	--	Yes	Yes	N/A	Yes	No	Low/moderate
Kampiire, 2012	--	Yes	--	N/A	--	--	Moderate
Kumarasamy, 2008a	--	Yes	Yes	N/A	Yes	No	Low/moderate
Kumarasamy, 2008b	--	Yes	--	N/A	Yes	--	Low/moderate
Manfredi, 2006	No[2]	Yes	Yes	N/A	Yes	No	Low/moderate
Mankhatitham, 2011	Yes	Yes	Yes	No	No	No	Low/moderate
Modayil, 2010	--	Yes	Yes	N/A	No	No	Low/moderate
Nunez, 2002	Yes	Yes	Yes	No	No	No	Low/moderate
Obiako, 2012	--	Yes	--	N/A	No	No	Low/moderate
Patel, 2006	Yes	Yes	Yes	N/A	No	No	Low
Richie, 2006	--	--	--	N/A	No	No	Low/moderate
Sanne, 2006					No	No	Low
Sivadasan, 2009	--	--	Yes	N/A	No	No	Low/moderate
Srirangaraj, 2010	--	--	Yes	N/A	No	No	Low/moderate
Sulkowski, 2002	No[3]	Yes	--	N/A	Yes	No	Moderate/high
Swaminathan, 2011	Yes	Yes	Yes	--	No	No	Low/moderate
Tukei, 2012	--	Yes	Yes	N/A	No	--	Low/moderate
van den Berg-Wolf, 2008	Yes	Yes	Yes	No	No	No	Low/moderate
Van Leth, 2004	Yes	Yes	Yes	Yes	No	No	Low
Wester, 2010	Yes	Yes	Yes	No	No	No	Low/moderate
Zhou, 2006	--	Yes	Yes	N/A	No	No	Low/moderate

1. Imbalanced for sex, CD4, and viral load
2. Imbalanced for disease stage
3. Imbalanced for HCV co-infection

N/A, not applicable

Supplementary Table S3: GRADE review - Adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	Other considerations	Nevirapine	Efavirenz	Relative (95% CI)	Absolute		
Treatment discontinuation												
18	randomised trials and cohort studies	no serious risk of bias[1,2]	serious[3]	no serious indirectness	no serious imprecision	None	613/11221	315/6291	OR 2.18 (1.86 to 2.56)	53 more per 1000 (from 39 more to 69 more)	⊕⊕⊕O MODERATE	CRITICAL
Hepatotoxicity - overall (assessed with: symptom and laboratory monitoring)												
23	randomised trials and cohort studies	no serious risk of bias[1,2]	very serious[4]	no serious indirectness	no serious imprecision	none	535/11481	256/4706	OR 2.51 (2.04 to 3.1)	72 more per 1000 (from 51 more to 97 more)	⊕⊕OO LOW	IMPORTANT
Hepatotoxicity - severe (assessed with: symptom and laboratory monitoring)												
16	randomised trials and cohort studies	no serious risk of bias[1,2]	serious[5]	no serious indirectness	no serious imprecision	none	249/9202	97/9221	OR 3.25 (2.54 to 4.17)	23 more per 1000 (from 16 more to 32 more)	⊕⊕⊕O MODERATE	CRITICAL
Skin - any (assessed with: symptom and laboratory monitoring)												
19	randomised trials and cohort studies	no serious risk of bias[1,2]	serious[6]	no serious indirectness	no serious imprecision	none	707/10386	177/3886	OR 1.80 (1.51 to 2.17)	32 more per 1000 (from 19 more to 46 more)	⊕⊕⊕O MODERATE	IMPORTANT
Skin - severe (assessed with: symptom and laboratory monitoring)												
15	randomised trials and cohort studies	no serious risk of bias[1,2]	very serious[7]	no serious indirectness	no serious imprecision	none	217/10574	38/2714	OR 3.68 (2.50 to 5.39)	30 more per 1000 (from 16 more to 47 more)	⊕⊕OO LOW	CRITICAL
Severe hypersensitivity reaction (assessed with: symptom and laboratory monitoring)												
9	randomised trials and cohort studies	no serious risk of bias[1,2]	no serious inconsistency[8]	no serious indirectness	no serious imprecision	none	272/8340	72/2220	OR 2.18 (1.63 to 2.90)	36 more per 1000 (from 19 more to 56 more)	⊕⊕⊕O MODERATE	CRITICAL
CNS - overall (assessed with: symptom monitoring)												
13	randomised trials and cohort studies	no serious risk of bias[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	285/6177	404/2269	OR 0.31 (0.26 to 0.38)	115 fewer per 1000 (from 102 fewer to 125 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
CNS - severe (assessed with: symptom monitoring)												
11	randomised trials and cohort studies	no serious risk of bias[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/5853	62/1619	OR 0.29 (0.18 to 0.46)	27 fewer per 1000 (from 20 fewer to 31 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Neurology (assessed with: symptom monitoring)												
10	randomised trials and cohort studies	no serious risk of bias[1,2]	serious	no serious indirectness	serious[9]	none	196/5663	84/1592	OR 0.88 (0.66 to 1.17)	6 fewer per 1000 (from 17 fewer to 8 more)	⊕⊕OO LOW	IMPORTANT
Lipid changes (assessed with: symptom and laboratory monitoring)												
7	randomised trials and cohort studies	no serious risk of bias[1,2]	serious[10]	serious[11]	serious[12]	none	105/5715	48/1693	OR 0.85 (0.59 to 1.23)	4 fewer per 1000 (from 11 fewer to 6 more)	⊕OOO VERY LOW	IMPORTANT

[1] Only 1 RCT reported allocation concealment
[2] Baseline prognostic factors balanced; non-differential loss to follow up.
[3] 4 studies reported odds ratios in the opposite direction to the pooled estimate, but only 1 of these was statistically significant. However, a further 5 studies reported odds ratios with confidence intervals consistent with either an increase or a decrease in the risk of adverse events, and several studies had non-overlapping confidence intervals.
[4] 7 of 23 studies reported odds ratios in the opposite direction to the pooled estimate; however, none of these were statistically significant. A further 3 studies reported odds ratios with confidence intervals consistent with either an increase or a decrease in the risk of adverse events.
[5] 4 of 16 studies reported odds ratios in the other direction to the pooled estimate; however, none of these were statistically significant.
[6] 1 study (138 patients) reported increased skin toxicity associated with EFV use; however, 8 studies reported odds ratios with confidence intervals consistent with either an increase or a decrease in the risk of adverse events.
[7] 3 studies reported odds ratios in the other direction to the pooled estimate; only one of these was statistically significant. However, a further 6 studies included odds ratios for which the confidence intervals were consistent with either an increase or a decrease in the risk of adverse events.
[8] 1 study suggested a greater tendency towards HSR with EFV, but this was based on a single event. All other studies indicated either a statistically significant association or a strong tendency towards a statistically significant association between NVP use and a greater likelihood of severe hypersensitivity reaction.
[9] Rated down because lower bound is consistent with a 44% reduction in neurological complications.
[10] Non-overlapping confidence intervals for several studies.
[11] Different markers of lipid abnormalities were used by different studies.
[12] Result consistent with a 41% decrease or a 23% increase in risk of adverse events.

Supplementary Table S4: GRADE review - Children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nevirapine	Efavirenz	Relative (95% CI)	Absolute		
Hepatotoxicity (assessed with: Laboratory)												
3	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	12/393 (3.1%)	4/260 (1.5%)	not pooled	not pooled	⊕OOO VERY LOW	CRITICAL
								0%		not pooled		
Skin toxicity												
2	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	24/262 (9.2%)	10/234 (4.2%)	not pooled	not pooled	⊕OOO VERY LOW	IMPORTANT
								0%		not pooled		
CNS												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	13/171 (7.6%)	25/177 (14.1%)	not pooled	not pooled	⊕OOO VERY LOW	IMPORTANT
								0%		not pooled		
Lipid abnormalities												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	11/171 (6.4%)	0/177 (0%)	not pooled	not pooled	⊕OOO VERY LOW	IMPORTANT
Discontinuation												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/259 (3.9%)	17/3031 (0.6%)	not pooled	not pooled	⊕⊕OO LOW	CRITICAL
								0%		not pooled		