Appendix

Appendix Table 1. Search strategy

1	hiv.af.
2	human immunodeficiency virus.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, nm, kf, px, rx, ui]
3	acquired immunodeficiency syndrome.af.
4	hiv aids.af.
5	1 or 2 or 3 or 4
6	stroke.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, nm, kf, px, rx, ui]
7	(myocardial infarction or heart attack).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, nm, kf, px, rx, ui]
8	cardiac death.af.
9	cerebrovascular disease.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, nm, kf, px, rx, ui]
10	(ischemic heart disease or Ischaemic heart disease).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, nm, kf, px, rx, ui]
11	(cardiovascular disease or cvd).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, dv, nm, kf, px, rx, ui]
12	6 or 7 or 8 or 9 or 10 or 11
13	5 and 12
14	limit 13 to human
15	limit 14 to english language
16	Limit 15 to yr= "2000 – Current"
17	remove duplicates from 16

Note: The searches were executed in the following four databases: (1) EBM Reviews - Cochrane Central Register of Controlled Trials <June 2018>, (2) EBM Reviews - Cochrane Database of Systematic Reviews <2005 to July 11, 2018>, (3) Embase <1974 to 2018 July 17>, (4) Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily <1946 to July 17, 2018>

Study selection

The excluded studies included several key CVD review articles,[1–8] and aggregate clinical trial studies,[9–12] whose bibliographies were screened for identification of additional relevant studies. We also excluded a number of potentially eligible records when more comprehensive or updated results for the same participants and risk comparison were published in another report;[13–16] risk associations were reported in a way that would not allow for pairwise grouping with other studies reporting similar associations to facilitate pooling of results;[17–21] or results were reported as number of events or unadjusted risk estimates only.[22–25]

Note: the references cited in the paragraph above are listed at the end of the appendix

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Appendix Table 2. Characteristics of included studies

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
LaFleur *et al* 2017[64]	Cohort	USA	ATV-cohort: 12 months Non-ATV: 13 months	HIV+	ATV-cohort: 1,529 (96) Non-ATV: 7,971 (92)	50 years	MI	ATV exposure vs. not exposed	HR[β]
Drozd *et al* 2017[42]	Cohort	North America	HIV+: 4.5 years HIV-: 19.7 years	HIV+/HIV- (NA-ACCORD / ARIC)	HIV+: 28,912 (81) HIV-: 14,308 (44)	HIV+: 80% were < 50 years HIV-: 27% were < 50 years	Type 1 MI	HIV+ vs. HIV-**	IRR[β]
Rosenblatt *et al* 2016a[65]	Cohort	USA	EFV-cohort: 23.2 months EFV-free: 19.3 months	HIV+	EFV-cohort: 11,978 (86) EFV-free: 10,234 (79)	EFV-cohort: 40.2 years EFV-free: 40.7 years	MI	EFV exposure vs. not exposed	HR[β]
Rosenblatt *et al* 2016b[66]	Cohort	USA	ATV-cohort: 24 months ATV-free: 21 months	HIV+	ATV-cohort: 2,437 (76) ATV-free: 19,774 (84)	ATV-cohort: 41.0 years ATV-free: 40.4 years	MI	ATV exposure vs. not exposed	HR[β]
Sabin *et al* 2016[53]	Cohort	Multi-national	7.0 (4.4-11.1) years[α]	HIV+	49,717 (74)	38 (32-44) years[α]	MI	Current ABC exposure vs. not current (1999-2013)	IRR[β]
Salinas *et al* 2016[54]	Cohort	USA	1996-2012 (follow-up)	HIV+	8,168 (97)	46 (40-53) years[α]	AMI	VL at ART initiation ≥ 100,000 copies/mL vs. < 100,000	HR[β]
Desai *et al* 2015[67]	Cohort	USA	~6.7 years	HIV+	24,510 (98)	46.5	MI	Current exposure to ABC vs. not currently exposed Current exposure to DDI vs. not currently exposed Current exposure to ATV vs. not currently exposed Current exposure to TDF vs. not currently exposed Current exposure to LPV vs. not currently exposed Current exposure to FTC vs. not currently exposed Current exposure to 3TC vs. not currently exposed Current exposure to d4T vs. not currently exposed Current exposure to ZDV vs. not currently exposed Current exposure to IDV vs. not currently exposed	OR[β] / HR[β]

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
								Current exposure to NFV vs. not currently exposed Current exposure to SQV vs. not currently exposed Current exposure to RTV vs. not currently exposed Current exposure to EFV vs. not currently exposed Current exposure to NVP vs. not currently exposed	
Klein *et al* 2015[71]	Cohort	USA	HIV+: 4.8years HIV-: 5.8 years	HIV+/HIV-	282,368 (91)	HIV+: 41 years HIV-: 40 years	MI	HIV+ vs HIV-	IRR[β]
Palella *et al* 2015[55]	Cohort	USA	~3.9 years	HIV+	16,733 (81)	Reported proportion of individuals by age categories	MI	Recent ABC use vs. non-recent use	HR[β]
Rasmussen *et al* 2015[56]	Cohort	Denmark	HIV+: 55,050–57,631 PYs HIV-: 638,204–659,237 PYss	HIV+/HIV-	HIV+: 5,897 (76) HIV-: 53,073 (76)	HIV+: 36.8 years[α] HIV-: 36.8 years[α]	MI	HIV+ vs. HIV-	IRR[β]
Drozd *et al* 2014[57]	Cohort	USA	1996-2012 (follow-up) NR	HIV+ HIV+	18,155 (NR) 17,626 (79)	NR Reported proportion of individuals by age categories	MI Primary MI	Current HIV RNA (log (copies/mL)+1) CD4 < 200 vs ≥ 200	OR[β] HR[β]
Silverberg *et al* 2014[72]	Cohort	USA	HIV+: 4.5 years HIV-: 5.4 years	HIV+/HIV-	HIV+: 22,081 (90.6) HIV-: 230,069 (90.5)	Reported proportion of individuals by age categories	MI	ART-treated HIV+ vs. HIV- ART-untreated HIV+ vs. HIV- Recent HIV RNA (per 1 log increase) Prior ART (yes vs no) Duration of PI use per year increase Duration of NNRTI use per year increase	IRR[β]
Freiberg *et al* 2013 [3]	Cohort	USA	5.9 years[α]	HIV+/HIV-	HIV+: 27,350 (97.3) HIV-: 55,109 (97.2)	HIV+: 48.2 years HIV-: 48.8 years	AMI	HIV+ vs. HIV- Recent CD4 < 200 (yes/no) Recent PI use (yes/no)	HR[β]
Lang *et al* 2012[51]	Nested case control	France	4.0 years	HIV+	Cases: 289 (88.9) Controls: 884 (89.1)	Cases: 47 (41-54) years[α]	MI	Current ABC vs not current HIV RNA per log10 increase	OR[β]

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
						Controls: 46 (40-54) years[α]			
Bedimo *et al* 2011[12]	Cohort	USA	3.9 years [α]	HIV+	19,424 (98)	46 years [α]	AMI	Cumulative ABC HAART per year of exposure Current ABC HAART vs. neither ABC/TDF Cumulative ARV per year of exposure	HR[β]
Choi *et al* 2011[24]	Cohort	USA	4.5 years[α]	HIV+	10,931 (98)	46 to 49 years (within subgroups by ART use)	MI	Recent ABC vs. not recent ABC or TDF	HR[β]
Durand *et al* 2011[52]	Cohort	Canada	4.0 years	HIV+/HIV-	HIV+: 7,053 (78); HIV-: 27,681 (78)	HIV+: 39.5 years HIV-: 39.7 years	AMI	HIV+ vs. HIV-	HR[β]
	Nested case control			HIV+	Cases: 125 (91.2); Controls: 1,084 (92.2)	Cases: 49.0 years Controls: 47.5 years	AMI	ABC exposure vs. no exposure Recent ABC vs. not recent DDI exposure vs. no exposure Recent DDI vs. not recent TDF exposure vs. no exposure Recent TDF vs. not recent ATV exposure vs. no exposure Recent ATV vs. not recent Recent LPV vs. not recent Recent RTV vs. not recent Recent EFV vs. not recent NVP exposure vs. no exposure Recent NVP vs. not recent FTC exposure vs. no exposure Recent FTC vs. not recent Recent 3TC vs. not recent d4T exposure vs. no exposure Recent d4T vs. not recent ZDV exposure vs. no exposure Recent ZDV vs. not recent Recent IDV vs. not recent	OR[β]

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
								NFV exposure vs. no exposure Recent NFV vs. not recent SQV exposure vs. no exposure Recent SQV vs. not recent	
Carman *et al* 2011[63]	Cohort	USA	1998-2007 (follow-up)	HIV+	66,286 (NR)	NR	AMI	Recent ABC use vs. no use Recent PI use vs. no use	IRR[β]
Lang *et al* 2010b[43]	Cohort	France	2000-2006 (follow-up)	HIV+/ general population	HIV+: ~ 74,958 General population: unclear	35 to 64 years	MI	HIV+ vs general population	SMR
Lang *et al* 2010a[11]	Nested case control	France	2000-2006 (follow-up)	HIV+	Cases: 289 (89) Controls: 884 (89)	Cases: 47 (41-54) years[α] Controls: 46 (40-54) years[α]	MI	Recent ABC exposure vs. no exposure Cumulative ABC exposure vs. no exposure Cumulative DDI per year of exposure Cumulative TDF per year of exposure Cumulative ZVD per year of exposure Cumulative EFV per year of exposure Cumulative NVP per year of exposure Cumulative LPV + RTV per year of exposure Cumulative NFV per year of exposure Cumulative 3TC exposure per year Cumulative d4T exposure per year	OR[β]
Obel *et al* 2010[8]	Cohort	Denmark	~ 6.5 years	HIV+	2,952 (76.4)	39.1 (33.0-46.6) years[α]	MI	ABC exposure vs. no exposure	IRR[β]
Worm *et al* 2010[58]	Cohort	Multi-national	5.8 (3.9-7.5) years[α]	HIV+	33,308 (74)	With MI: 49 (43-65) years[α] Without MI: 44 (38-50) years[α]	MI	Cumulative ABC exposure per year	Relative rate[β]

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
								Recent TDF exposure vs. not recent Cumulative TDF exposure per year Recent DDI exposure vs. not recent Cumulative LPV-RTV exposure per year Cumulative NFV exposure per year Cumulative NVP exposure per year Cumulative EFV exposure per year	
Triant *et al* 2010[68]	Cohort	USA	5.1 years[α]	HIV+	6,517 (69)	46 years	AMI	CD4 count < 200/mm^3 vs ≥ 200 Nadir CD4 per 50/mm^3 increase VL > 100,000 copies/mL vs. ≤ 100,000 HIV RNA per log 10 increase ART per year since first ART use TDF use vs. none ABC use vs. none DDI use vs. none FTC use vs. none d4T use vs. none NVP use vs. none ATV use vs. none NFV use vs. none SQV use vs. none	OR[β]
Triant *et al* 2009[69]	Cohort	USA	HIV+: 6.0 years HIV-: 5.8 years	HIV+/HIV-	HIV+: 487 (62.8) HIV-: 69,870 (45.6)	HIV+/HIV-: Reported proportion by age categories	AMI	HIV+ vs. HIV-	OR[β]
D:A:D Study Group *et al* 2008a[13]	Cohort	Multi-national	5.1 years[α]	HIV+	33,347 (74)	With MI: 49 (range: 24-92) years[α] Without MI: 44 (range: 12-95) years[α]	MI	Recent ABC exposure vs. never exposed to ABC Recent DDI exposure vs. never exposed Cumulative DDI exposure per year	Relative rate[β]

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
								Recent ZDV exposure vs. never exposed Recent ZDV exposure vs. not recent Cumulative ZDV exposure per year Recent 3TC exposure vs. not recent Cumulative 3TC exposure per year Recent d4T exposure vs. not recent Recent d4T exposure vs. never exposed Cumulative d4T exposure per year	
D:A:D Study Group *et al* 2008b[59]	Cohort	Multi-national	4.5 years[α]	HIV+	28,985 (NR)	Reported by calendar period	MI	Cumulative exposure to PIs per year Cumulative exposure to NNRTIs per year	Relative rate[β]
D:A:D Study Group *et al* 2007[7]	Cohort	Multi-national	4.5 years[α]	HIV+	23,437 (76)	39 (34-45) years[α]	MI	Nadir CD4 per 50 cells/mm^3 increase	Relative rate[β]
Obel *et al* 2007[60]	Cohort	Denmark	HIV+: 6.9years[α] HIV-: 8.1 years[α]	HIV+/ HIV-	HIV+: 3,953 (76.8) HIV-: 373,856 (76.3)	HIV+: 36.8 (30.8-44.6) years[α] HIV-: 36.4 (30.6-44.0) years[α]	MI	HIV+, on HAART+ vs. HIV- HIV+ not on HAART- vs. HIV-	IRR[β]
Kwong *et al* 2006[70]	Cohort	USA and Netherlands	3.49 (range: 0.02-18.46) years[α]	HIV+	18,603 (82.63)	36 (range: 18-92) years[α]	MI	PI per year of exposure NNRTI per year of exposure HAART per year of exposure	RR[β]
Mary-Krause *et al* 2003[6]	Cohort	France	With MI: 28 (18-39) months[α] Without MI: 33 (15-48) months[α]	HIV+ men	34,976 (100)	With MI: 41.9 years Without MI: 37.7 years	MI	Exposure to PI	Relative hazard[β]
Holmberg *et al* 2002[61]	Cohort	USA	~ 3.1 years	HIV+	5,672 (82)	42.6 years	MI	PI use (yes vs no)	HR[β]

Author, year	Study type	Location	Mean follow-up	Population	Sample size (% male)	Mean age	Outcome	Relevant risk association(s) examined	Effect measure
Rickerts *et al* 2000*[62]	Cohort	Germany	24.6 ± 18.1 months	HIV+	2,861 (78)	36.6 ± 9.5 years	MI	Prior HAART (yes vs. no)	OR[β]

Legend: [α], median (including lower and upper quartiles, where reported); [β], adjusted estimate; *, extracted data from the ART era only; **, this was a general population comparison group and may not have consisted of HIV- individuals only; Note: a superscript alongside the author name/year is used to denote the reference number of the study; **ABC**, abacavir; **AMI**, acute myocardial infarction; **ARIC**, Atherosclerosis Risk in Communities; **ART**, antiretroviral therapy; **ATV**, atazanavir; **DDI**, didanosine; **d4T**, stavudine; **EFV**, efavirenz; **FTC**, emtricitabine; **HAART**, highly active antiretroviral therapy; **HR**, Hazard ratio; **IDV**, indinavir; **IRR**, incidence rate ratio; **LPV**, lopinavir; **LPV-RTV**, lopinavir-ritonavir; **MI**, myocardial infarction; **NA-ACCORD/ARIC**, North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD)/Atherosclerosis Risk in Communities (ARIC) cohorts; **NFV**, nelfinavir; **NNRTI**, non-nucleoside reverse transcriptase inhibitor; **NR**, not reported; **NRTI**, nucleoside reverse transcriptase inhibitor; **NVP**, nevirapine; **OR**, Odds ratio; **PI**, protease inhibitor; **RR**, relative risk; **RTV**, ritonavir; **SMR**, standardized morbidity ratio; **SQV**, saquinavir; **TDF**, tenofovir; **VL**, viral load; **ZDV**, zidovudine; **3TC**, lamivudine

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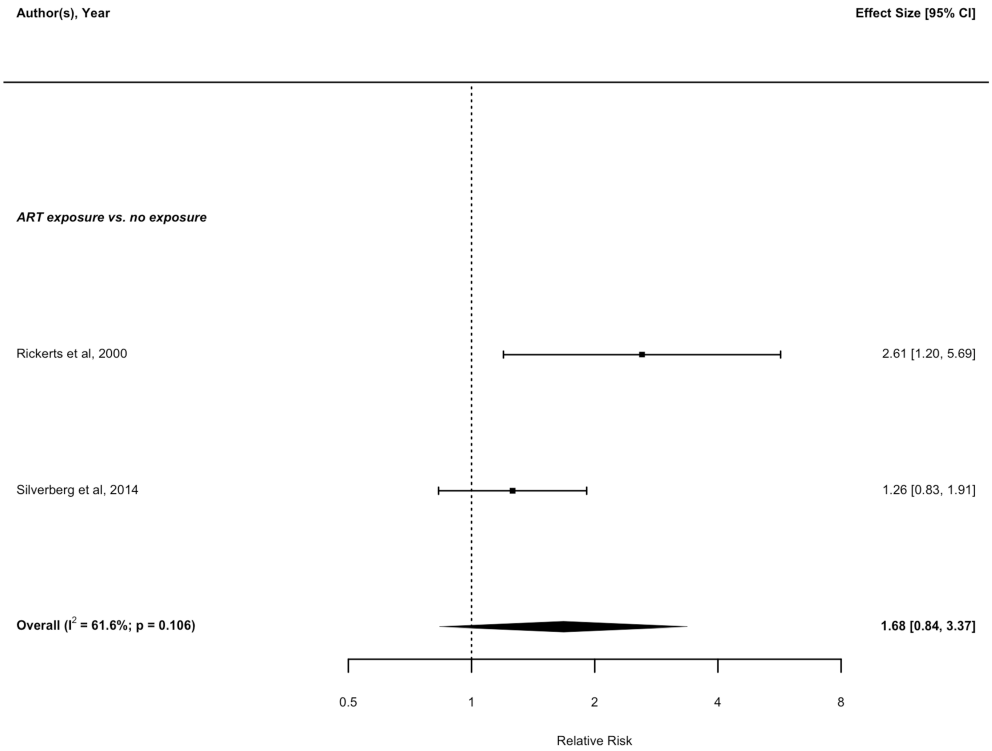
Appendix Table 3. Risk of bias in the included studies

Author, year	Publication type	Study design	Clearly defined eligibility criteria	Description of participants/ group(s) selection	Potential for bias in case/group representation	Comparability among group(s) based on design or analysis	Adequate exposure/outcome ascertainment	Sufficient follow-up for outcome occurrence?	Funding source
LaFleur *et al* 2017[64]	Journal	Cohort (R)	+	+	No	+	-	-	Public. industry
Drozd *et al* 2017[42]	Journal	Cohort (P & R)	+	+	Yes*	-	+	+	Public
Rosenblatt *et al* 2016a[65]	Journal	Cohort (R)	+	+	No	+	-	+	Industry
Rosenblatt *et al* 2016b[66]	Journal	Cohort (R)	+	+	No	+	-	+	Industry
Sabin *et al* 2016[53]	Journal	Cohort (P)	+	+	No	+	+	+	Public, industry
Salinas *et al* 2016[54]	Journal	Cohort (P)	+	+	No	+	-	+	Public
Desai *et al* 2015[67]	Journal	Cohort (R)	+	+	No	+	-	+	Public
Klein *et al* 2015[71]	Journal	Cohort (R)	+	+	No	+	+	+	Private, industry
Palella *et al* 2015[55]	Abstract	Cohort (P & R)	+	+	No	-	+	+	-
Rasmussen *et al* 2015[56]	Journal	Cohort (P)	+	+	No	+	-	+	Public, private
Drozd *et al* 2014[57]	Abstract	Cohort (P)	-	+	No	-	+	-	Public
Silverberg *et al* 2014[72]	Journal	Cohort (R)	+	+	No	+	+	+	Private, industry
Freiberg *et al* 2013[3]	Journal	Cohort (P)	+	+	No	+	+	+	Public
Lang *et al* 2012[51]	Journal	Nested case-control	+	+	No	+	+	+	Public
Bedimo *et al* 2011[12]	Journal	Cohort (R)	+	+	No	+	-	+	-
Choi *et al* 2011[24]	Journal	Cohort (R)	+	+	No	+	-	+	Public
Durand *et al* 2011[52]	Journal	Cohort (R), & nested case-control	+	+	No	+	-	+	Industry
Carman *et al* 2011[63]	Abstract	Cohort (R)	-	+	-	-	-	+	-

Author, year	Publication type	Study design	Clearly defined eligibility criteria	Description of participants/ group(s) selection	Potential for bias in case/group representation	Comparability among group(s) based on design or analysis	Adequate exposure/outcome ascertainment	Sufficient follow-up for outcome occurrence?	Funding source
Lang *et al* 2010a[11]	Journal	Nested case-control	+	+	No	+	+	+	Public
Lang *et al* 2010b[43]	Journal	Cohort (R)	+	+	No	-	+	+	Public
Obel *et al* 2010[8]	Journal	Cohort (P)	+	+	No	+	-	+	Public, private
Worm *et al* 2010[58]	Journal	Cohort (P)	+	+	No	+	+	+	Public, industry
Triant *et al* 2010[68]	Journal	Cohort (R)	+	+	No	+	-	+	Public
Triant *et al* 2009[69]	Journal	Cohort (R)	+	+	No	+	-	+	Public
D:A:D Study Group *et al* 2008a[13]	Journal	Cohort (P)	+	+	No	+	+	+	Public, industry
D:A:D Study Group *et al* 2008b[59]	Journal	Cohort (P)	+	+	No	+	+	+	Public, industry
D:A:D Study Group *et al* 2007[7]	Journal	Cohort (P)	+	+	No	+	+	+	Public, industry
Obel *et al* 2007[60]	Journal	Cohort (P)	+	+	No	+	-	+	Public, private
Kwong *et al* 2006[70]	Journal	Cohort (R)	+	+	No	+	-	+	Public, industry
Mary-Krause *et al* 2003[6]	Journal	Cohort (R)	+	+	No	+	+	+	Public
Holmberg *et al* 2002[61]	Journal	Cohort (P)	+	+	No	-	+	+	Public
Rickerts *et al* 2000[62]	Journal	Cohort (P)	+	+	No	+	+	+	-

Legend: + means this is clearly described and adequate; - means this is unclear, inadequate or not reported; *, The HIV+ cohort (NA-ACCORD study) was compared to a general population cohort from a different study (Atherosclerosis Risk in Communities [ARIC] study); Note: a superscript alongside the author name/year is used to denote the reference number of the study; **NA**, Not applicable; **P**, Prospective; **R**, Retrospective



Appendix Figure A1. Forest plot of the meta-analysis of the risk of MI associated with any exposure to antiretroviral therapy
Legend: CI, Confidence interval

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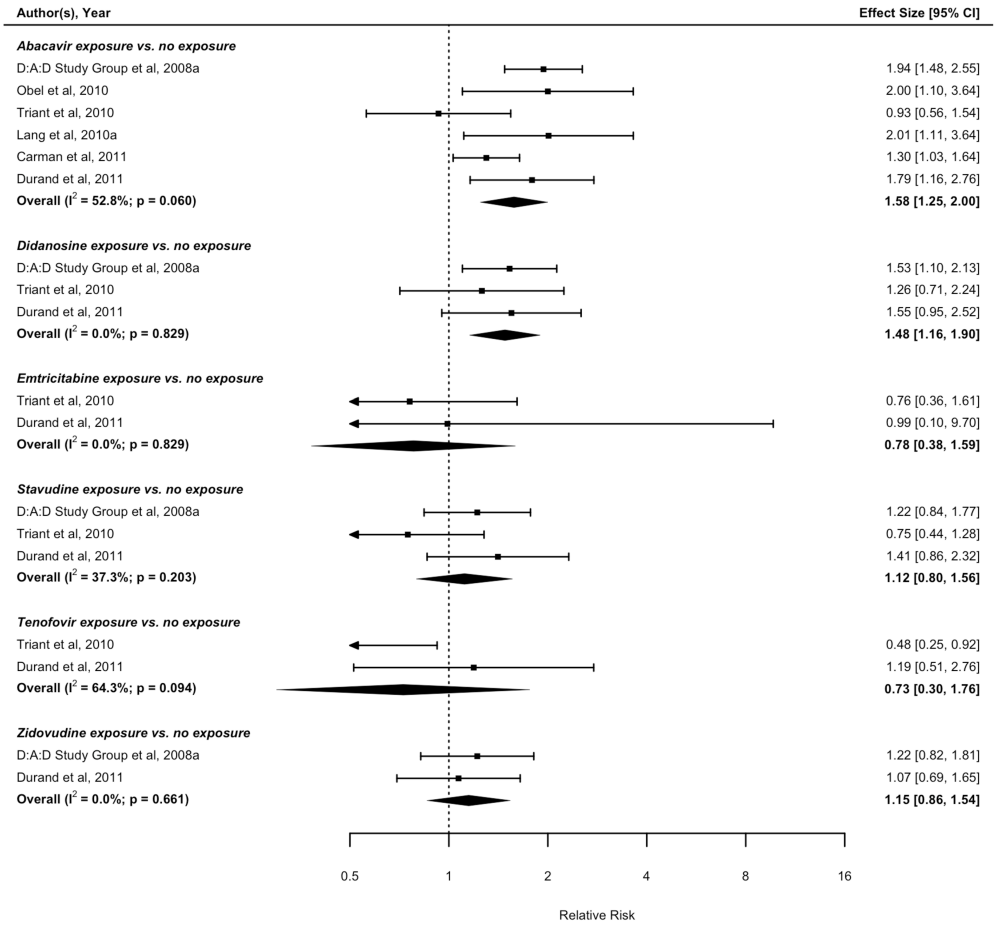
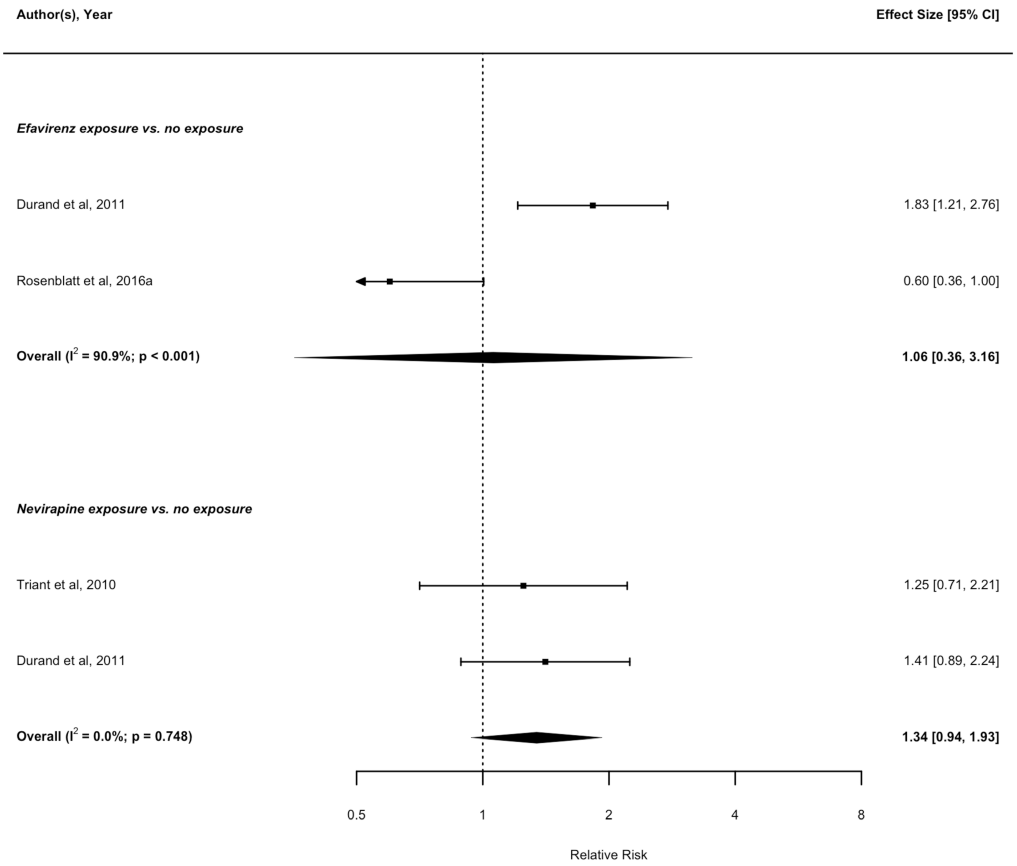
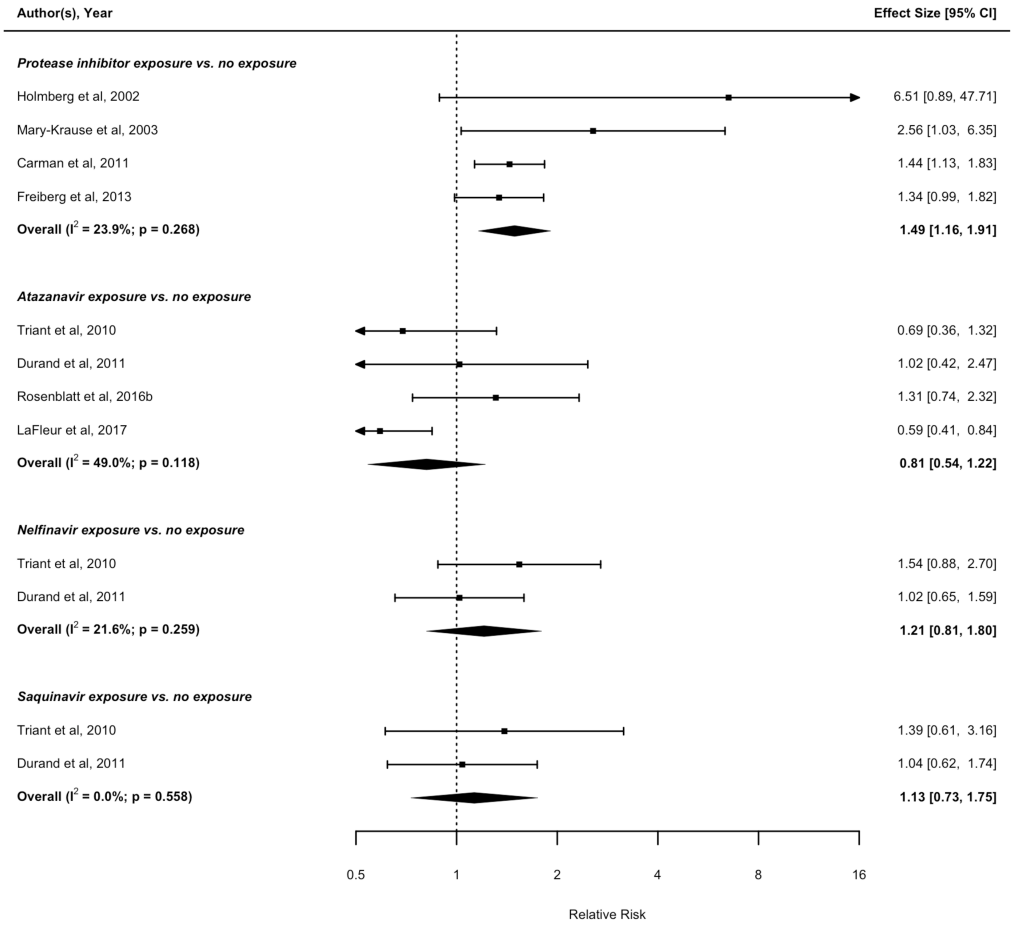


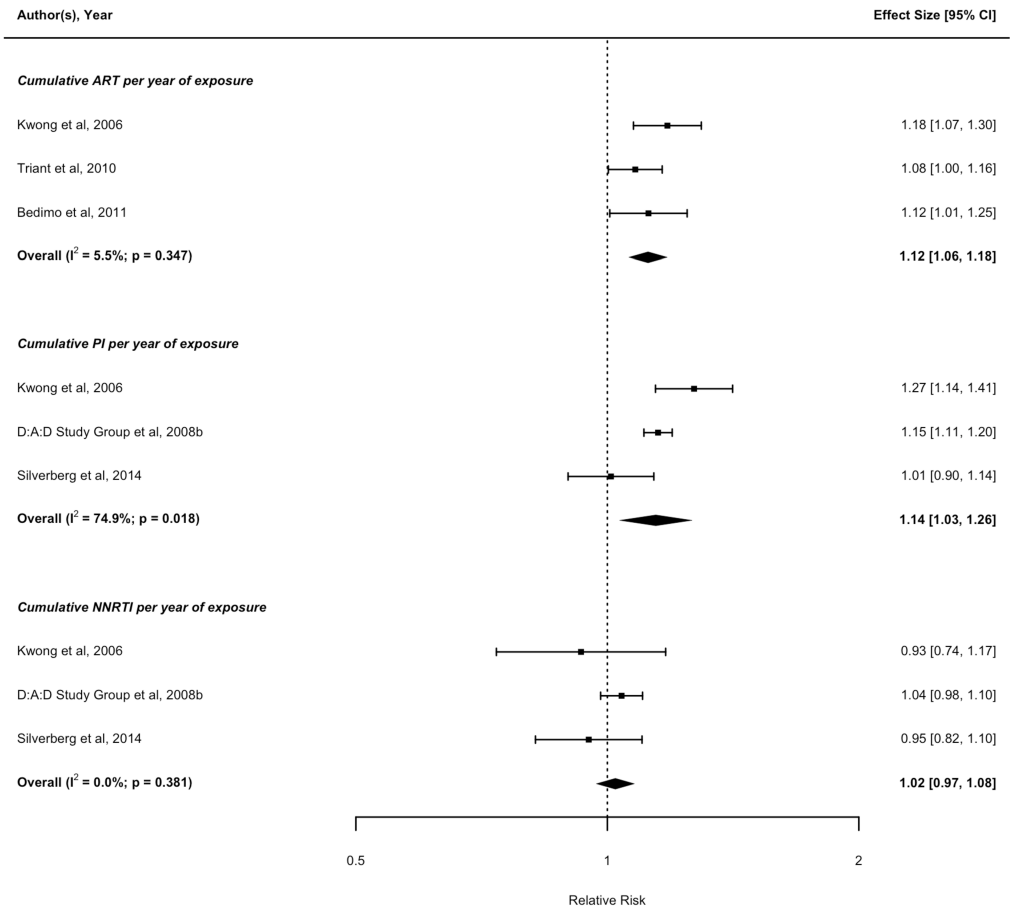
Appendix Figure A2. Forest plot of the meta-analysis of the risk of MI associated with any exposure to drugs of the NRTI class
Legend: CI, Confidence interval



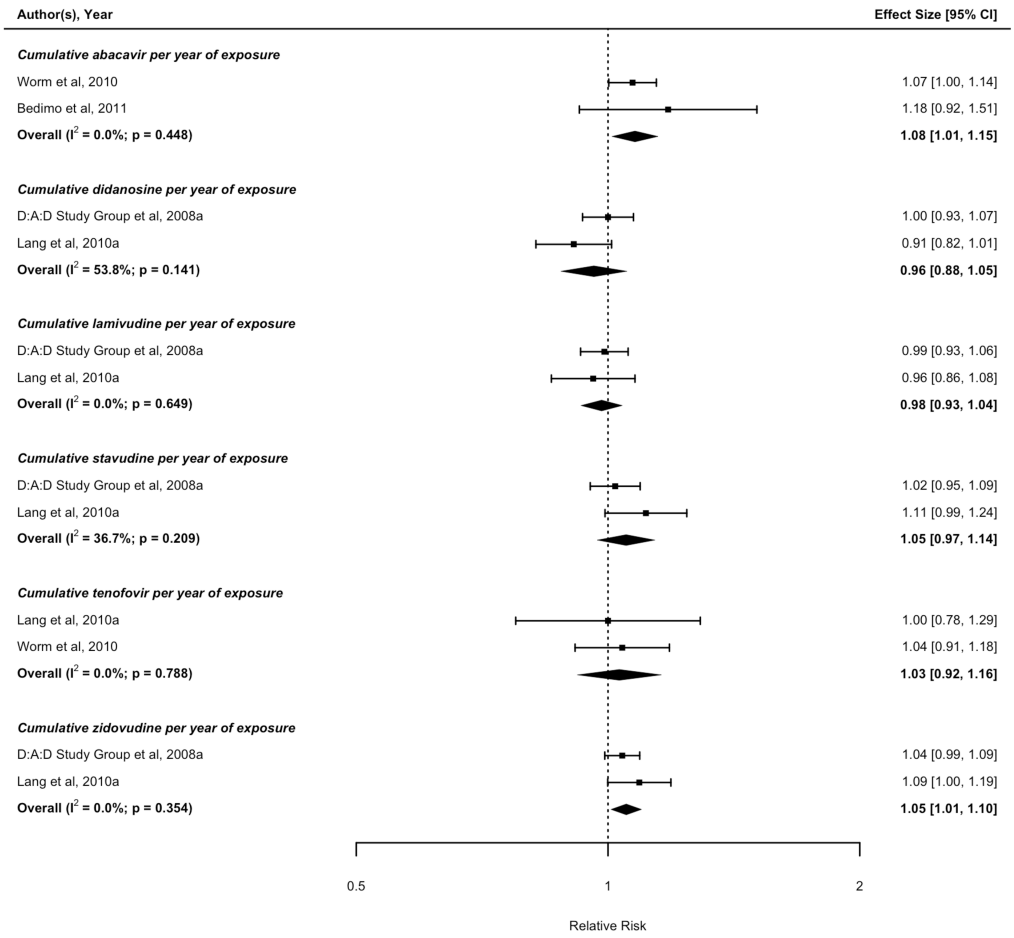
Appendix Figure A3. Forest plot of the meta-analysis of the risk of MI associated with any exposure to drugs of the NNRTI class
Legend: CI, Confidence interval



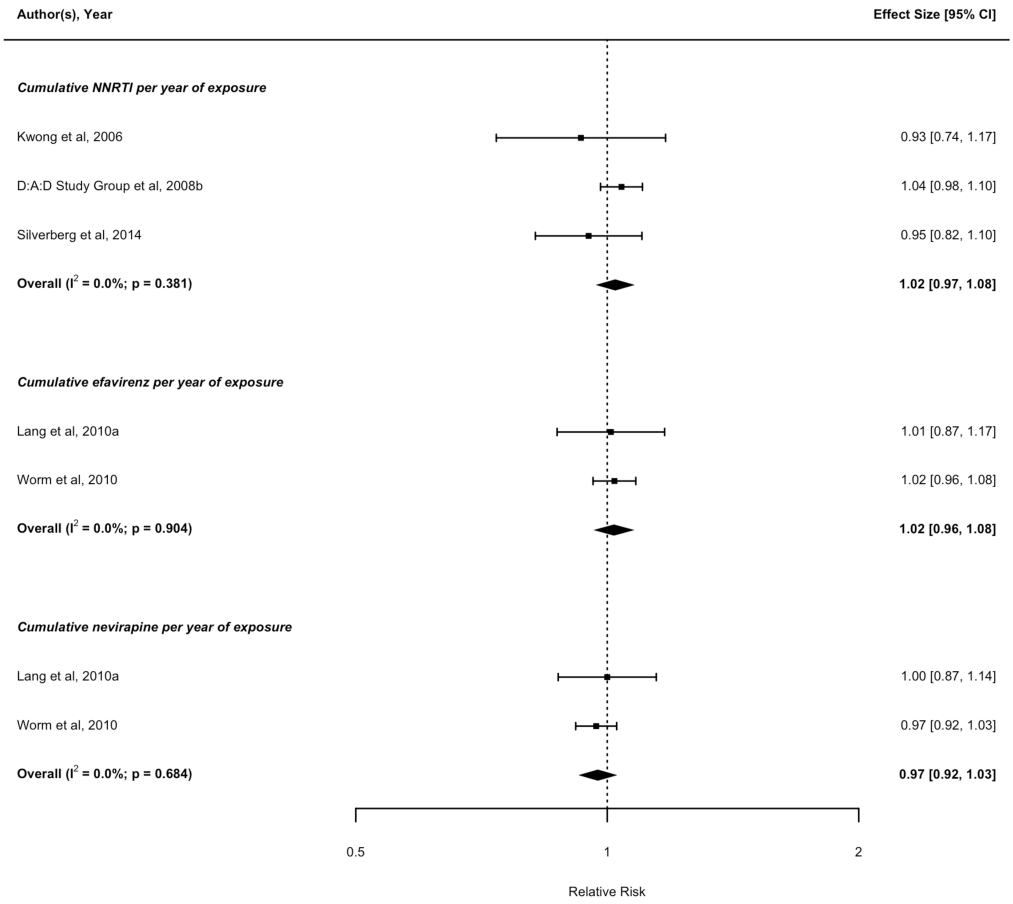
Appendix Figure A4. Forest plot of the meta-analysis of the risk of MI associated with any exposure to protease inhibitors (both as a class and individually)
Legend: CI, Confidence interval



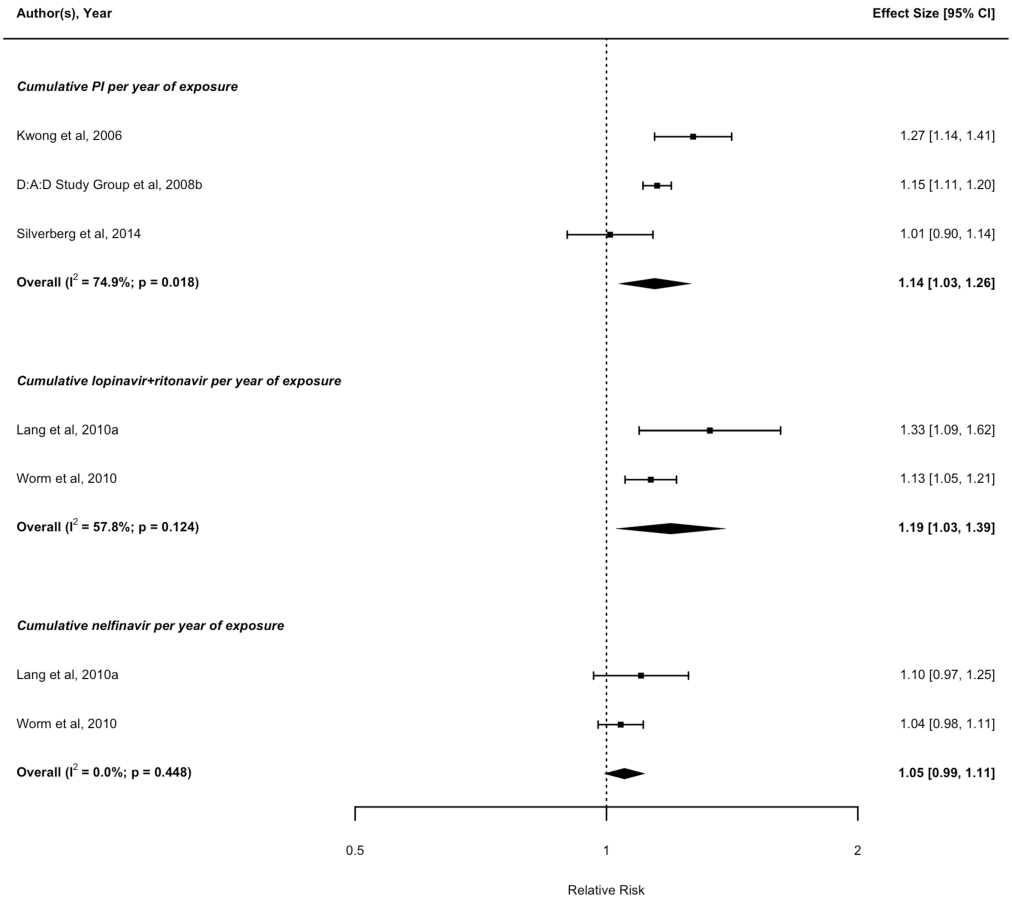
Appendix Figure A5. Forest plot of the meta-analysis of the risk of MI associated with cumulative exposure to antiretroviral therapy (ART) including class of ART
Legend: ART, Antiretroviral therapy; CI, Confidence interval; NNRTI, Non-nucleoside reverse transcriptase inhibitors; PI, Protease inhibitors



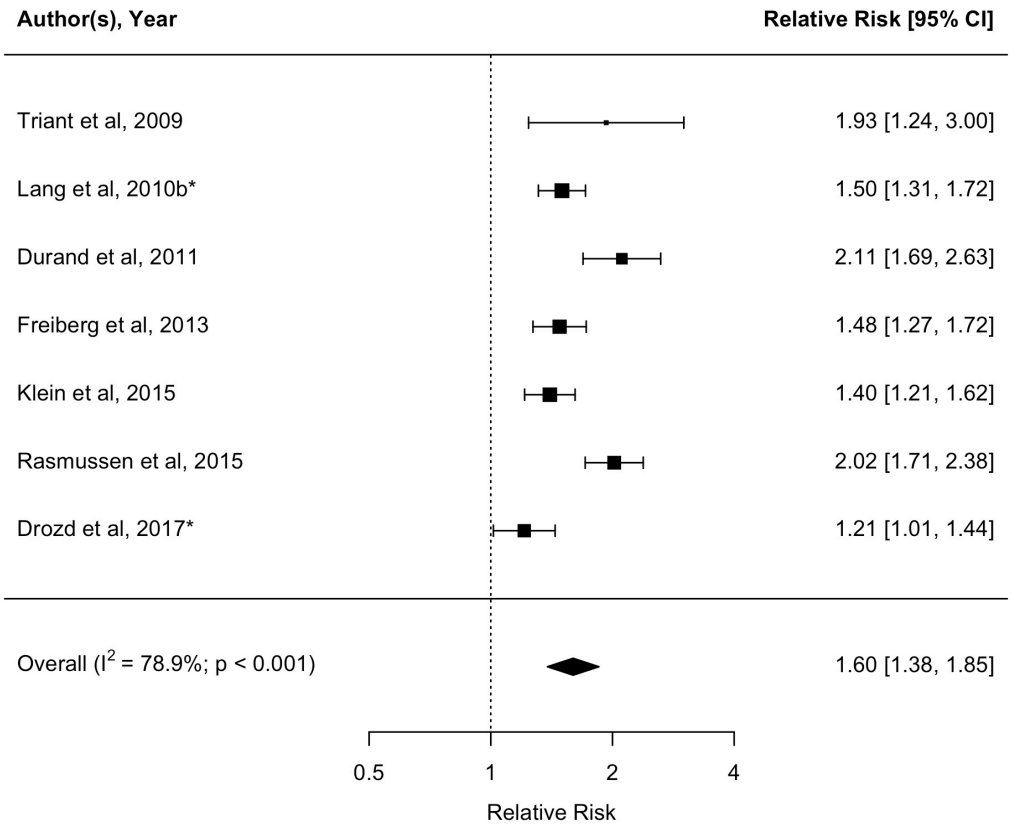
Appendix Figure A6. Forest plot of the meta-analysis of the risk of MI associated with cumulative exposure to drugs of the NRTI class
Legend: CI, Confidence interval



Appendix Figure A7. Forest plot of the meta-analysis of the risk of MI associated with cumulative exposure to NNRTI (both as a class and individually)
Legend: CI, Confidence interval; NNRTI, Non-nucleoside reverse transcriptase inhibitors

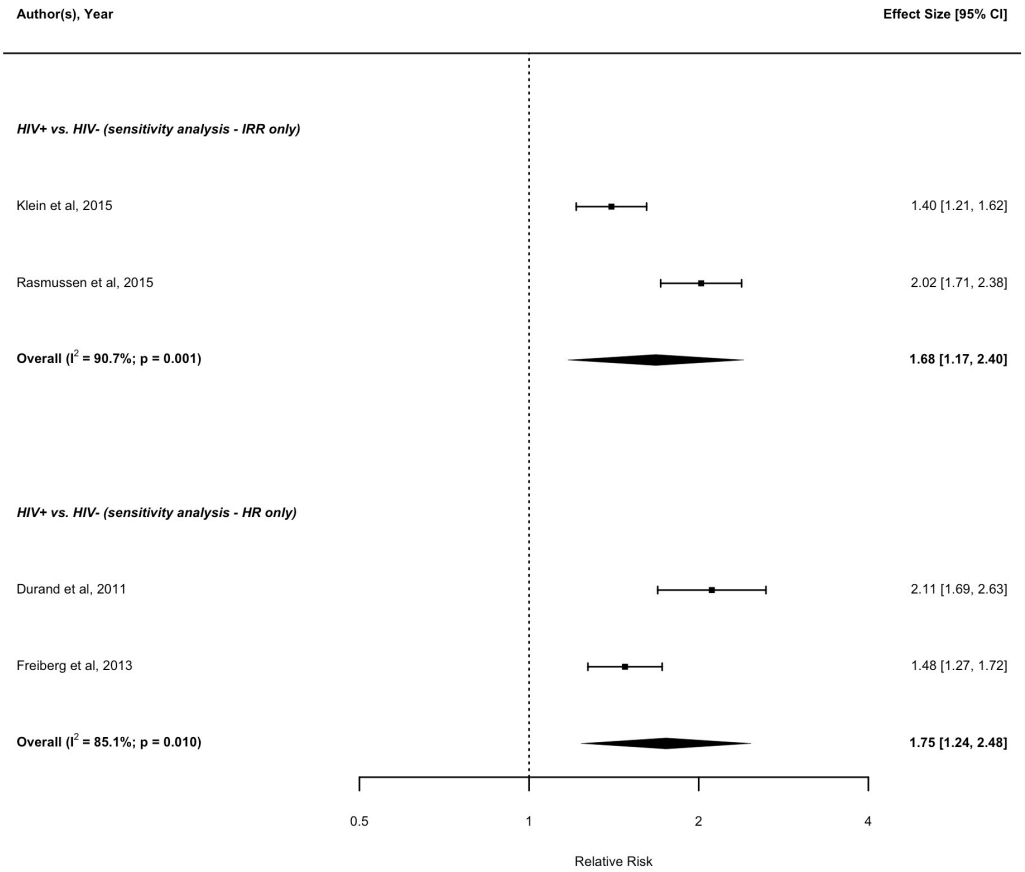


Appendix Figure A8. Forest plot of the meta-analysis of the risk of MI associated with cumulative exposure to protease inhibitors (both as a class and individually)
Legend: CI, Confidence interval; PI, Protease inhibitors



Appendix Figure S1. Forest plot of the sensitivity analysis for the meta-analysis of the risk of MI associated with HIV infection, where two additional studies involving a general population comparison group were included

Legend: *, This study had a 'general population' comparison group and may not have consisted of HIV-negative individuals only; CI, Confidence interval



Appendix Figure S2. Forest plot of the sensitivity analyses for the meta-analysis of the risk of MI associated with HIV infection, where estimates reported using similar relative effect measures were pooled

Legend: CI, Confidence interval; HR, Hazard ratio; IRR, Incidence rate ratio

Appendix References (for study selection section only)

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