

Systematic literature search: PICO questions

2.1 Questions and PICO criteria

Databases: Medline, Embase, Cochrane Library,

Conference abstracts:

- IAS Conference on HIV Pathogenesis and Treatment
- International AIDS Conference
- Conference on Retroviruses and Opportunistic Infections (CROI)
- European Conference on Clinical Aspects and Treatment of HIV Infection (EACS)
- Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)
- International Congress on Drug Therapy in HIV Infection
- British HIV Association Annual Conference (BHIVA)
- International Workshop on Co-morbidities and Adverse Drug Reactions in HIV
- International Workshop on HIV Resistance
- International Workshop on Clinical Pharmacology of HIV and Hepatitis

Date parameters:

- databases: October 2011–date
- conference abstracts: October 2011–date

When to start

Study design: Systematic reviews (SRs), randomised control trials (RCTs), Observational.

Chronic HIV infection:

Population: HIV infected naïve to antiretroviral therapy (ART)

Intervention: starting ART early: (i) at CD4 count >350 cells/μL; (ii) at CD4 count >500 cells/μL; (iii) immediately at time of diagnosis

Comparator: starting ART CD4 count <350 cells/μL

Outcomes: death, AIDS, non-AIDS co-morbidities, drug adverse events, drug resistance, HIV transmission/incidence

Questions:

1. In a person with CD4 count >350 cells/μL (or >500 cells/μL), is there net long-term benefit (in terms of clinical endpoints AIDS, cirrhosis, end stage renal failure, myocardial infarction, cardiovascular disease, cancer, all-cause mortality) from starting ART immediately, compared with deferring ART initiation to when the CD4 count is 350 cells/μL?
2. In a person with a CD4 count >350 cells/μL (or >500 cells/μL), what is the cost (financial, toxicity, resistance) vs. benefit (decreased AIDS, death, non-AIDS endpoints and transmission) from starting ART immediately, compared with deferring ART initiation to when the CD4 count is 350 cells/μL or lower?

Primary HIV infection

Population: Acute/primary HIV infection

Intervention: immediate ART therapy (short course or continued)

Comparator: no therapy, starting ART as per chronic infection

Outcomes: time to CD4 count <350 cells/ μ L, death, AIDS, HIV transmission/incidence, post-treatment control of viral load

Question:

3. Is there benefit in starting patients diagnosed with primary/acute HIV infection immediately on ART compared to waiting till CD4 count <350 or <500 cells/ μ L? What is the magnitude of this benefit?

Advanced HIV disease

Population: HIV infection, advanced disease

Intervention: immediate ART

Comparator: deferred ART

Outcomes: Death, new AIDS diagnosis, immune reconstitution disorders

Question:

4. Should patients presenting with severe AIDS-defining opportunistic infections start ART immediately, or defer until after starting treatment of OI (including cryptococcal meningitis, tuberculosis)?

ART to prevent transmission

Population: HIV infected with HIV negative partner, sero-discordance

Intervention: Immediate ART

Comparator: starting ART at CD4 count <350 cells/ μ L

Outcome: HIV transmission to negative partner

Question:

5. What is the cost (financial, toxicity, resistance) vs. benefit (reduced AIDS, death, non-AIDS endpoints and reduced transmission) of starting treatment earlier [similar question to 3 above]

What to start with

Study design: SRs, RCTs,

Preferred regimen/choice of third agent

Population: HIV infected naïve to ART and (i) VL >100,000; (ii) VL <100,000 copies/ml

Intervention: ritonavir/darunavir or ritonavir/atazanavir, raltegravir, rilpivirine, cobicistat/elvitegravir and dolutegravir containing combination ART

Comparator: efavirenz (or atazanavir/ritonavir or darunavir/ritonavir or raltegravir or cobicistat/elvitegravir) containing combination ART

Outcome: virological suppression (VL <50 copies/ml), virological failure, discontinuing regimen secondary to AEs (or for any reason), grade 3/4 AEs, emergent HIV drug resistance

Question:

6. How does each third drug compare to efavirenz (or other comparator) in terms of efficacy and safety?

Preferred regimen/choice of NRTI backbone

Population: HIV infected naïve to ART

Intervention: abacavir/lamivudine containing combination ART

Comparator: tenofovir/emtricitabine containing combination ART

Outcomes: virological suppression (VL <50 copies/ml), virological failure, discontinuing regimen secondary to AEs, grade 3/4 AEs, HIV drug resistance

Questions:

7. What are the advantages and disadvantages of using tenofovir/emtricitabine (Truvada) vs. abacavir/lamivudine (Kivexa)?

8. Do fixed-dose combination tablets (Atripla, Eviplera, Stribild, Truvada, Kivexa) lead to improved adherence, lower viral load, less resistance, improved quality of life or increased cost-effectiveness in comparison to separate tabs?

Novel treatment strategies

Population: HIV infected naïve to ART

Intervention: (i) PI mono-therapy; (ii) NRTI sparing and PI based dual regimens (raltegravir + either darunavir/r or atazanavir/r or Kaletra; maraviroc + either darunavir/r or atazanavir/r)

Comparator: standard triple combination ART

Outcome: virological suppression (VL <50 copies/ml), virological failure, discontinuing regimen secondary to AEs (or any other reason), grade 3/4 AEs, HIV drug resistance

Question:

9. What are the advantages and disadvantages of each of these strategies compared to standard triple combination ART?

Supporting patients on ART

Switching therapy (simplification)

Study design: SRs, RCTs

Population: Antiretroviral therapy experienced, treatment experienced, virologically suppressed, viral load <50 copies/ml

Intervention: protease inhibitor monotherapy, switch third agent, switch NRTI backbone

Comparator: continuing current therapy

Outcome: virological suppression, virological failure, discontinuing regimen, grade3/4 AEs, HIV drug resistance

Questions:

10. What are the benefits and disadvantages (and what is the overall balance) of simplifying from conventional ART to protease inhibitor monotherapy?

11. In patients suppressed on conventional ART (2 NRTIs + EFV or boosted PI), what are the relative advantages and disadvantages of switching to alternative third agents or NRTI backbone (e.g. PI/r → NNRTI, alternative PI/r or Integrase inhibitor, NNRTI → PI/r, alternative NNRTI or integrase inhibitor)?

Managing virological failure

Low level viraemia and recurrent viral load blips

Virological failure with treatment options

Virological failure with limited treatment options

Study designs: SRs, RCTs, observational

Population: ART experienced, virological failure, dual and triple class HIV drug resistance, viral load blips

Intervention: switching ART, continuing lamivudine(3TC) or emtricitabine (FTC), salvage therapy, etravirine, raltegravir, maraviroc, tipranavir, darunavir

Outcomes: virological suppression, virological failure, discontinuing regimen secondary to AEs, Grade3/4 AEs, CD4 count, HIV drug resistance

Questions:

12. What is the risk of virological failure with or without resistance in patients with more than one detectable viral load above different thresholds? Compared with patients with VL continuously < 50 ?
13. Should nucleosides be included in regimens after virological failure?

ART in special populations

Study design: SRs, RCTs, observational

HIV associated neurocognitive disorders

Population: HIV associated neurocognitive impairment/disorders, HIV associated dementia

Intervention: Antiretroviral therapy (list all ART drugs)

Outcomes: progressive HIV neurocognitive disorders

Question:

14. Does the choice of specific drugs or regimens lead to improved neurocognitive outcomes in any specific circumstances?

Non-AIDS co-morbidities: chronic kidney disease, cardiovascular disease, bone disease (osteoporosis/osteopenia)

Population: chronic kidney disease, estimated glomerular filtration rate <60 mls/min/1.73sqm, cardiovascular disease, myocardial infarction

Intervention: ART, tenofovir, abacavir, protease inhibitors (lopinavir clinical events, CVD clinical events)

Outcomes: bone disease, fracture, psychiatric illness, hyperlipidaemia

Question:

15. Are there patients with evidence of bone disease, hyperlipidaemia or psychiatric disease in whom treatment with specific antiretrovirals should be avoided?

BHIVA ART Guideline **2014 update**: SEARCH PROTOCOL: main databases search

Search 1 :When to Initiate ART

Covers Questions 1-5 including to prevent transmission

Component	Description
Review area	Timing of ART initiation
Objectives	To assess the benefits and risks of earlier rather than later initiation of ART
Populations	Chronic HIV Infection, Primary HIV infection, Advanced HIV disease, HIV infected with HIV negative partner (sero-discordance)
Interventions	Antiretroviral therapy (all drugs) , HAART
Comparisons/ aspects covered by search	Initiation : at diagnosis: at CD4 count >350 : at CD4 count >500
Outcomes	To be decided by writing groups
Study designs	SRs, RCTs, observational studies, risk, economic
Exclusions	Animal studies, letters, editorials, comments, case reports, Non English studies.
How the information was searched	Databases: Medline, Embase, Cochrane Library Language: restrict to English only date parameters : database entry date September2011-current
Search terms and date searched	HIV + ARVS + early/late starting See attached Medline strategy document for details :searched 6 August 2014
Search results	Medline/premedline= 619 Embase= 756 Cochrane = 150 Total= 1525 Total deduplicated/title sifted = 798
The review strategy (The methods that will be used to review the evidence, outlining exceptions and subgroups.)	To be decided by writing groups
Key papers	

Database: Ovid MEDLINE(R) Daily Update <August 05, 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

-
- 1 exp HIV/ (85063)
 - 2 exp HIV Infections/ (235109)
 - 3 HIV Long-Term Survivors/ (586)
 - 4 AIDS Serodiagnosis/ (6138)
 - 5 (aids adj3 virus).ti,ab. (1906)
 - 6 (HIV or HIV1 or HIV2 or hiv-1 or hiv-2).ti,ab. (235894)
 - 7 (human immunodeficiency virus or human immunodeficiency virus or human immunodeficiency virus or human immune-deficiency virus).ti,ab. (71696)
 - 8 (human immun\$ adj3 deficiency virus).ti,ab. (463)
 - 9 (acquired immunodeficiency syndrome or acquired immunodeficiency syndrome or acquired immuno-deficiency syndrome or acquired immune-deficiency syndrome).ti,ab. (19801)
 - 10 (acquired immun\$ adj3 deficiency syndrome).ti,ab. (5185)
 - 11 or/1-10 (322994)
 - 12 exp child/ or exp infant/ or (child\$ or neonat\$ or infant\$).ti. (2153644)
 - 13 exp Adult/ or adult\$.ti. (5692890)
 - 14 12 not 13 (1469295)
 - 15 11 not 14 (305918)
 - 16 anecdotes as topic/ (4579)
 - 17 letter/ (851412)
 - 18 news/ (164234)
 - 19 editorial/ (362762)
 - 20 exp historical article/ (324027)
 - 21 comment/ or case report/ (2275763)
 - 22 (letter or comment\$).ti. (98137)
 - 23 or/16-22 (3380269)
 - 24 23 not (randomized controlled trial/ or randomized controlled trial as topic/ or random\$).ti,ab. (3367094)
 - 25 exp animal model/ (421766)
 - 26 exp rodentia/ (2693413)
 - 27 exp animal experimentation/ (6435)
 - 28 exp animals, laboratory/ (733144)
 - 29 exp animals/ not humans/ (3975659)
 - 30 (rat or rats or monkey\$ or rodent\$ or dog or dogs or cat or cats or feline or canine or primate\$ or macaque\$ or mouse or mice).ti. (1395702)
 - 31 or/24-30 (7959228)
 - 32 15 not 31 (229126)
 - 33 exp Anti-Retroviral Agents/ (66115)
 - 34 Antiretroviral Therapy, Highly Active/ (17628)
 - 35 HAART.ti,ab. (10584)
 - 36 (NRTI\$ or NNRTI\$).ti,ab. (4041)
 - 37 ((antiretroviral or anti-retroviral) adj2 (therap\$ or treatment\$ or agent\$ or drug\$)).ti,ab. (38567)
 - 38 ((nucleoside or non-nucleoside) adj1 reverse transcriptase inhibitor\$).ti,ab. (4194)
 - 39 ((protease or HIV integrase) adj1 inhibitor\$).ti,ab. (27937)
 - 40 (didanosine or lamivudine or nevirapine or stavudine or zidovudine or indinavir or nelfinavir or ritonavir or saquinavir or emtricitabine or rilpivirine or lopinavir or amprenavir or fosamprenavir or atazanavir or darunavir or tipranavir or maraviroc or enfuvirtide or raltegravir or etravirine or abacavir or tenofovir or efavirenz or Kaletra or Combivir or Truvada or Atripla or Trizivir or Sustiva).ti,ab. (28504)

- 41 (Stribild or eviplera or kivexa or elvitegravir or ziagen or emtriva or epivir or complera or retrovir or viread or stocrin or intelence or viramune or edurant or reyataz or prezista or telzir or norvir or aptivus or celsentri or dolutegravir or tivicay or vitekta or isentress).ti,ab. (944)
- 42 (Trii or epzicom or zerit or amdoxovir or videx or resciptor or delavirdine or lersivirine or crixivan or invirase or lexiva or viracept or fuzeon or selzentry or cenicriviroc or ibalizumab).ti,ab. (1006)
- 43 ((anti-HIV or anti-aids) adj1 (drug\$ or agent\$)).ti,ab. (2335)
- 44 or/33-43 (110614)
- 45 32 and 44 (60120)
- 46 ((early or earlier or immediat\$ or delay\$ or defer\$ or later) adj3 (begin\$ or start\$ or therap\$ or ART or HAART or anti-retroviral\$ or antiretroviral\$ or initiat\$ or commence\$ or timepoint\$ or time or timing)).ti,ab. (90158)
- 47 ((early or earlier or immediat\$ or delay\$ or defer\$ or later) adj3 (didanosine or lamivudine or nevirapine or stavudine or zidovudine or indinavir or nelfinavir or ritonavir or saquinavir or emtricitabine or rilpivirine or lopinavir or amprenavir or fosamprenavir or atazanavir or darunavir or tipranavir or maraviroc or enfuvirtide or raltegravir or etravirine or abacavir or tenofovir or efavirenz or Kaletra or Combivir or Truvada or Atripla or Trizivir or Sustiva or Stribild or eviplera or kivexa or elvitegravir or ziagen or emtriva or epivir or complera or retrovir or viread or stocrin or intelence or viramune or edurant or reyataz or prezista or telzir or norvir or aptivus or celsentri or dolutegravir or tivicay or vitekta or isentress or Trii or epzicom or zerit or amdoxovir or videx or resciptor or delavirdine or lersivirine or crixivan or invirase or lexiva or viracept or fuzeon or selzentry or cenicriviroc or ibalizumab)).ti,ab. (442)
- 48 (early or earlier or immediat\$ or delay\$ or defer\$).ti. (292767)
- 49 (when to start or when to begin or when to initiate or when to commence or wait to start or wait to begin or wait to initiate or wait to commence).ti,ab. (1531)
- 50 ((timepoint\$ or timing or time) adj2 (initiat\$ or start\$ or begin\$ or commence\$)).ti,ab. (7020)
- 51 or/46-50 (375153)
- 52 Drug Administration Schedule/ or Time Factors/ (1085417)
- 53 *CD4 Lymphocyte Count/ (1326)
- 54 52 and 53 (183)
- 55 51 or 54 (375298)
- 56 45 and 55 (3214)
- 57 systematic review/ (0)
- 58 meta-analysis/ (50192)
- 59 meta-analysis as topic/ (13928)
- 60 (meta-analy\$ or metanaly\$ or metaanaly\$ or meta analy\$ or meta regression).ti,ab. (68413)
- 61 ((systematic\$ or evidence) adj2 (review\$ or overview\$)).ti,ab. (78764)
- 62 (reference list\$ or bibliograph\$ or hand search\$ or manual search\$ or relevant journals).ab. (26429)
- 63 (search strategy or search criteria or systematic search or study selection or data extraction).ab. (28200)
- 64 (search\$ adj4 literature).ti,ab. (29347)
- 65 (medline or pubmed or cochrane or psychlitt or psychlit or psychinfo or cinahl or science citation index or bids or cancerlit).ab. (84573)
- 66 cochrane.jw. (11109)
- 67 ((multiple treatment\$ or indirect or mixed) adj2 comparison\$).ti,ab. (1441)
- 68 or/57-67 (206294)
- 69 randomized controlled trial.pt. (380240)
- 70 controlled clinical trial.pt. (88960)

- 71 randomi#ed.ti,ab. (385723)
- 72 placebo.ab. (156778)
- 73 randomly.ab. (217817)
- 74 clinical trials as topic.sh. (171327)
- 75 trial.ti. (129810)
- 76 or/69-75 (946010)
- 77 epidemiologic studies/ (6023)
- 78 exp case control studies/ (674512)
- 79 exp cohort studies/ (1372942)
- 80 cross-sectional studies/ (180379)
- 81 case control.ti,ab. (80099)
- 82 (cohort adj (study or studies or analys\$)).ti,ab. (94643)
- 83 ((follow up or observational or uncontrolled or non randomi#ed) adj (study or studies)).ti,ab. (88378)
- 84 ((longitudinal or retrospective or prospective) and (study or studies or review or analys\$ or cohort\$)).ti,ab. (675158)
- 85 cross sectional.ti,ab. (176787)
- 86 or/77-85 (1986304)
- 87 Economics/ (27046)
- 88 "Value of Life"/ (5916)
- 89 "Costs and Cost Analysis"/ (41996)
- 90 exp Economics, Hospital/ (19630)
- 91 Economics, Nursing/ (3919)
- 92 Economics, Pharmaceutical/ (2552)
- 93 exp Economics, Medical/ (13624)
- 94 exp "Fees and Charges"/ (27174)
- 95 exp Budgets/ (12138)
- 96 budget\$.ti,ab. (19392)
- 97 cost\$.ti. (82996)
- 98 (economic\$ or pharmaco?economic\$).ti. (33660)
- 99 (price\$ or pricing\$).ti,ab. (25522)
- 100 (cost\$ adj2 (effectiv\$ or utilit\$ or benefit\$ or minimi\$ or unit\$ or estimat\$ or variable\$)).ab. (95845)
- 101 (financ\$ or fee or fees).ti,ab. (77615)
- 102 (value adj2 (money or monetary)).ti,ab. (1391)
- 103 or/87-102 (366762)
- 104 Multicenter Study/ (176272)
- 105 exp risk/ (846136)
- 106 odds ratio/ (61124)
- 107 exp survival analysis/ (188339)
- 108 or/104-107 (1132688)
- 109 68 or 76 or 86 or 103 or 108 (3659021)
- 110 56 and 109 (2006)
- 111 limit 110 to english language (1941)
- 112 (201109\$ or 201110\$ or 201111\$ or 201112\$ or 2012\$ or 2013\$ or 2014\$).ed. (2902617)
- 113 111 and 112 (619)

BHIVA ART Guideline: **2014 update** SEARCH PROTOCOL: main databases search

Search 2: ART firstline regimens

Covers questions 6-9

Component	Description
Review area	Preferred initial ART regimens
Objectives	Safety and efficacy of various different firstline regimens in ART naïve patients including choice of third agent
Populations	HIV infected, naïve to ART Adults – all questions
Interventions	All ARVS includes Fixed dose combinations, PI monotherapy , PI based dual therapy, NRTI sparing regimens
Comparisons/ aspects covered by search	
Outcomes	To be decided by writing groups
Study designs	SRs, RCTs,
Exclusions	Animal studies, letters, editorials, comments, case reports Non English studies.
How the information was searched	Databases: Medline, Embase, Cochrane Library Language: restrict to English only date parameters : September 2011 to current
Search terms and date searched	HIV + ARVS + naïve/ firstline See attached strategy document for details: searched 6 August 2014
Search results	Medline/premedline= 451 Embase= 579 Cochrane = 360 Total=1390 Total deduplicated/title sifted = 720
The review strategy (The methods that will be used to review the evidence, outlining exceptions and subgroups.)	
Key papers	

Database: Ovid MEDLINE(R) Daily Update <August 05, 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

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 - 7 (human immunodeficiency virus or human immunodeficiency virus or human immunodeficiency virus or human immune-deficiency virus).ti,ab. (71696)
 - 8 (human immun\$ adj3 deficiency virus).ti,ab. (463)
 - 9 (acquired immunodeficiency syndrome or acquired immunodeficiency syndrome or acquired immuno-deficiency syndrome or acquired immune-deficiency syndrome).ti,ab. (19801)
 - 10 (acquired immun\$ adj3 deficiency syndrome).ti,ab. (5185)
 - 11 or/1-10 (322994)
 - 12 exp child/ or exp infant/ or (child\$ or neonat\$ or infant\$).ti. (2153644)
 - 13 exp Adult/ or adult\$.ti. (5692890)
 - 14 12 not 13 (1469295)
 - 15 11 not 14 (305918)
 - 16 anecdotes as topic/ (4579)
 - 17 letter/ (851412)
 - 18 news/ (164234)
 - 19 editorial/ (362762)
 - 20 exp historical article/ (324027)
 - 21 comment/ or case report/ (2275763)
 - 22 (letter or comment\$).ti. (98137)
 - 23 or/16-22 (3380269)
 - 24 23 not (randomized controlled trial/ or randomized controlled trial as topic/ or random\$).ti,ab. (3367094)
 - 25 exp animal model/ (421766)
 - 26 exp rodentia/ (2693413)
 - 27 exp animal experimentation/ (6435)
 - 28 exp animals, laboratory/ (733144)
 - 29 exp animals/ not humans/ (3975659)
 - 30 (rat or rats or monkey\$ or rodent\$ or dog or dogs or cat or cats or feline or canine or primate\$ or macaque\$ or mouse or mice).ti. (1395702)
 - 31 or/24-30 (7959228)
 - 32 15 not 31 (229126)
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 - 34 Antiretroviral Therapy, Highly Active/ (17628)
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 - 37 ((antiretroviral or anti-retroviral) adj2 (therap\$ or treatment\$ or agent\$ or drug\$)).ti,ab. (38567)
 - 38 ((nucleoside or non-nucleoside) adj1 reverse transcriptase inhibitor\$).ti,ab. (4194)
 - 39 ((protease or HIV integrase) adj1 inhibitor\$).ti,ab. (27937)
 - 40 (didanosine or lamivudine or nevirapine or stavudine or zidovudine or indinavir or nelfinavir or ritonavir or saquinavir or emtricitabine or rilpivirine or lopinavir or amprenavir or fosamprenavir or atazanavir or darunavir or tipranavir or maraviroc or enfuvirtide or raltegravir

- or etravirine or abacavir or tenofovir or efavirenz or Kaletra or Combivir or Truvada or Atripla or Trizivir or Sustiva).ti,ab. (28504)
- 41 (Stribild or eviopera or kivexa or elvitegravir or ziagen or emtriva or epivir or complera or retrovir or viread or stocrin or intelence or viramune or edurant or reyataz or prezista or telzir or norvir or aptivus or celsentri or dolutegravir or tivicaay or vitekta or isentress).ti,ab. (944)
- 42 (Trii or epzicom or zerit or amdoxovir or videx or rescriptor or delavirdine or lersivirine or crixivan or invirase or lexiva or viracept or fuzeon or selzentry or cenicriviroc or ibalizumab).ti,ab. (1006)
- 43 ((anti-HIV or anti-aids) adj1 (drug\$ or agent\$)).ti,ab. (2335)
- 44 or/33-43 (110614)
- 45 (PI adj2 (dual or boosted or therapy or monotherapy or mono-therapy)).ti,ab. (653)
- 46 32 and (44 or 45) (60121)
- 47 naive.ti,ab. (53615)
- 48 ((firstline or first-line or first line or initial or start\$ or begin\$) adj2 (therap\$ or regim\$ or anti-retroviral\$ or antiretroviral\$ or agent\$ or drug\$ or HAART or ART)).ti,ab. (43670)
- 49 ((firstline or first-line or first line or initial) adj1 treatment).ti,ab. (28066)
- 50 or/47-49 (120368)
- 51 46 and 50 (8287)
- 52 systematic review/ (0)
- 53 meta-analysis/ (50192)
- 54 meta-analysis as topic/ (13928)
- 55 (meta-analy\$ or metanaly\$ or metaanaly\$ or meta analy\$ or meta regression).ti,ab. (68413)
- 56 ((systematic\$ or evidence) adj2 (review\$ or overview\$)).ti,ab. (78764)
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- 68 randomly.ab. (217817)
- 69 clinical trials as topic.sh. (171327)
- 70 trial.ti. (129810)
- 71 or/64-70 (946010)
- 72 63 or 71 (1093791)
- 73 51 and 72 (1947)
- 74 limit 73 to english language (1879)
- 75 (201109\$ or 201110\$ or 201111\$ or 201112\$ or 2012\$ or 2013\$ or 2014\$).ed. (2902617)
- 76 74 and 75 (451)

BHIVA ART Guideline: 2014 update SEARCH PROTOCOL: main databases search

Search 3: Switching/simplification of ART regimens

Covers Section 3 Questions 10 and 11

Component	Description
Review area	ART simplification/ switching options
Objectives	Safety and efficacy of switching drug therapy or simplifying drug regimens
Populations	HIV infected on HAART Adults – all questions
Interventions	All ARVS including PI monotherapy, alternative NRTI backbone, alternative third agents
Comparisons/ aspects covered by search	conventional HAART
Outcomes	To be decided by writing groups
Study designs	SRs, RCTs
Exclusions	Animal studies, letters, editorials, comments, case reports, Non English studies.
How the information was searched	Databases: Medline, Embase, Cochrane Library Language: restrict to English only date parameters : September 2011-current
Search terms and date searched	HIV + ARVS + switching/ simplification See attached strategy document for details : date of search 6 August 2014
Search results	Medline/premedline= 318 Embase= 390 Cochrane =263 Total=971 Total deduplicated/title sifted = 526
The review strategy (The methods that will be used to review the evidence, outlining exceptions and subgroups.)	
Key papers	

Database: Ovid MEDLINE(R) Daily Update <August 05, 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

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 - 6 (HIV or HIV1 or HIV2 or hiv-1 or hiv-2).ti,ab. (235894)
 - 7 (human immunodeficiency virus or human immunodeficiency virus or human immunodeficiency virus or human immune-deficiency virus).ti,ab. (71696)
 - 8 (human immun\$ adj3 deficiency virus).ti,ab. (463)
 - 9 (acquired immunodeficiency syndrome or acquired immunodeficiency syndrome or acquired immuno-deficiency syndrome or acquired immune-deficiency syndrome).ti,ab. (19801)
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 - 22 (letter or comment\$).ti. (98137)
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 - 24 23 not (randomized controlled trial/ or randomized controlled trial as topic/ or random\$).ti,ab. (3367094)
 - 25 exp animal model/ (421766)
 - 26 exp rodentia/ (2693413)
 - 27 exp animal experimentation/ (6435)
 - 28 exp animals, laboratory/ (733144)
 - 29 exp animals/ not humans/ (3975659)
 - 30 (rat or rats or monkey\$ or rodent\$ or dog or dogs or cat or cats or feline or canine or primate\$ or macaque\$ or mouse or mice).ti. (1395702)
 - 31 or/24-30 (7959228)
 - 32 15 not 31 (229126)
 - 33 exp Anti-Retroviral Agents/ (66115)
 - 34 Antiretroviral Therapy, Highly Active/ (17628)
 - 35 HAART.ti,ab. (10584)
 - 36 (NRTI\$ or NNRTI\$).ti,ab. (4041)
 - 37 ((antiretroviral or anti-retroviral) adj2 (therap\$ or treatment\$ or agent\$ or drug\$)).ti,ab. (38567)
 - 38 ((nucleoside or non-nucleoside) adj1 reverse transcriptase inhibitor\$).ti,ab. (4194)
 - 39 ((protease or HIV integrase) adj1 inhibitor\$).ti,ab. (27937)
 - 40 (didanosine or lamivudine or nevirapine or stavudine or zidovudine or indinavir or nelfinavir or ritonavir or saquinavir or emtricitabine or rilpivirine or lopinavir or amprenavir or fosamprenavir or atazanavir or darunavir or tipranavir or maraviroc or enfuvirtide or raltegravir

- or etravirine or abacavir or tenofovir or efavirenz or Kaletra or Combivir or Truvada or Atripla or Trizivir or Sustiva).ti,ab. (28504)
- 41 (Stribild or eviopera or kivexa or elvitegravir or ziagen or emtriva or epivir or complera or retrovir or viread or stocrin or intelence or viraamune or edurant or reyataz or prezista or telzir or norvir or aptivus or celsentri or dolutegravir or tivocay or vitekta or isentress).ti,ab. (944)
- 42 (Trii or epzicom or zerit or amdoxovir or videx or rescriptor or delavirdine or lersivirine or crixivan or invirase or lexiva or viracept or fuzeon or selzentry or cenicriviroc or ibalizumab).ti,ab. (1006)
- 43 ((anti-HIV or anti-aids) adj1 (drug\$ or agent\$)).ti,ab. (2335)
- 44 or/33-43 (110614)
- 45 (PI adj2 (dual or boosted or therapy or monotherapy or mono-therapy)).ti,ab. (653)
- 46 32 and (44 or 45) (60121)
- 47 ((stop\$ or change\$ or changing or discontinu\$ or interrupt\$ or withdraw\$ or substitut\$ or cessation or ceas\$) adj3 (third agent or backbone or treatment or regim\$ or therap\$ or drug\$ or anti-retroviral\$ or antiretroviral\$ or HAART or ART)).ti,ab. (116800)
- 48 ((stop\$ or change\$ or changing or discontinu\$ or interrupt\$ or withdraw\$ or substitut\$ or cessation or ceas\$) adj2 (didanosine or lamivudine or nevirapine or stavudine or zidovudine or indinavir or nelfinavir or ritonavir or saquinavir or emtricitabine or rilpivirine or lopinavir or amprenavir or fosamprenavir or atazanavir or darunavir or tipranavir or maraviroc or enfuvirtide or raltegravir or etravirine or abacavir or tenofovir or efavirenz or Kaletra or Combivir or Truvada or Atripla or Trizivir or Sustiva or Stribild or eviopera or kivexa or elvitegravir or ziagen or emtriva or epivir or complera or retrovir or viread or stocrin or intelence or viraamune or edurant or reyataz or prezista or telzir or norvir or aptivus or celsentri or dolutegravir or tivocay or vitekta or isentress or Trii or epzicom or zerit or amdoxovir or videx or rescriptor or delavirdine or lersivirine or crixivan or invirase or lexiva or viracept or fuzeon or selzentry or cenicriviroc or ibalizumab)).ti,ab. (969)
- 49 (maintenance adj3 (mono-therapy or therapy or regim\$ or monotherap\$)).ti,ab. (12104)
- 50 (switch\$ or simplif\$).ti,ab. (162197)
- 51 ((stop\$ or ceas\$ or cessation or discontinu\$ or withdraw\$) adj3 (staggered or simultaneous\$)).ti,ab. (379)
- 52 Withholding Treatment/ (9636)
- 53 or/47-52 (296301)
- 54 46 and 53 (6143)
- 55 systematic review/ (0)
- 56 meta-analysis/ (50192)
- 57 meta-analysis as topic/ (13928)
- 58 (meta-analy\$ or metanaly\$ or metaanaly\$ or meta analy\$ or meta regression).ti,ab. (68413)
- 59 ((systematic\$ or evidence) adj2 (review\$ or overview\$)).ti,ab. (78764)
- 60 (reference list\$ or bibliograph\$ or hand search\$ or manual search\$ or relevant journals).ab. (26429)
- 61 (search strategy or search criteria or systematic search or study selection or data extraction).ab. (28200)
- 62 (search\$ adj4 literature).ti,ab. (29347)
- 63 (medline or pubmed or cochrane or psychlit or psychlit or psychinfo or cinahl or science citation index or bids or cancerlit).ab. (84573)
- 64 cochrane.jw. (11109)
- 65 ((multiple treatment\$ or indirect or mixed) adj2 comparison\$).ti,ab. (1441)
- 66 or/55-65 (206294)
- 67 randomized controlled trial.pt. (380240)
- 68 controlled clinical trial.pt. (88960)
- 69 randomi#ed.ti,ab. (385723)

- 70 placebo.ab. (156778)
- 71 randomly.ab. (217817)
- 72 clinical trials as topic.sh. (171327)
- 73 trial.ti. (129810)
- 74 or/67-73 (946010)
- 75 66 or 74 (1093791)
- 76 54 and 75 (1640)
- 77 limit 76 to english language (1585)
- 78 (201109\$ or 201110\$ or 201111\$ or 201112\$ or 2012\$ or 2013\$ or 2014\$).ed.
(2902617)
- 79 77 and 78 (318)

BHIVA ART Guideline: 2014 update SEARCH PROTOCOL: main databases search

Search 4: Virological failure

Covers Questions 12 and 13

Component	Description
Review area	Managing Virological failure/drug resistance
Objectives	Risk of and management of patient with virological failure/ resistance
Populations	HIV infected on HAART with or at risk of virological failure/ resistance Adults – all questions
Interventions	All ARVS, salvage therapy
Comparisons/ aspects covered by search	conventional HAART
Outcomes	To be decided by writing groups
Study designs	SRs, RCTs, observational, risk
Exclusions	Animal studies, letters, editorials, comments, case reports, Non English studies.
How the information was searched	Databases: Medline, Embase, Cochrane Library Language: restrict to English only date parameters : September 2011-current searched 7 August 2014
Search terms and date searched	HIV + ARVS + resistance/ virological (treatment) failure See attached strategy document for details: originally searched 16/9/11
Search results	Medline/premedline= 760 Embase= 878 Cochrane = 197 Total=1832 Total deduplicated/title sifted = 1105
The review strategy (The methods that will be used to review the evidence, outlining exceptions and subgroups.)	
Key papers	

Database: Ovid MEDLINE(R) Daily Update <August 06, 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

-
- 1 exp HIV/ (85357)
 - 2 exp HIV Infections/ (236061)
 - 3 HIV Long-Term Survivors/ (591)
 - 4 AIDS Serodiagnosis/ (6151)
 - 5 (aids adj3 virus).ti,ab. (1910)
 - 6 (HIV or HIV1 or HIV2 or hiv-1 or hiv-2).ti,ab. (236882)
 - 7 (human immunodeficiency virus or human immunodeficiency virus or human immunodeficiency virus or human immune-deficiency virus).ti,ab. (71938)
 - 8 (human immun\$ adj3 deficiency virus).ti,ab. (465)
 - 9 (acquired immunodeficiency syndrome or acquired immunodeficiency syndrome or acquired immuno-deficiency syndrome or acquired immune-deficiency syndrome).ti,ab. (19850)
 - 10 (acquired immun\$ adj3 deficiency syndrome).ti,ab. (5196)
 - 11 or/1-10 (324147)
 - 12 exp child/ or exp infant/ or (child\$ or neonat\$ or infant\$).ti. (2168729)
 - 13 exp Adult/ or adult\$.ti. (5734127)
 - 14 12 not 13 (1479792)
 - 15 11 not 14 (307003)
 - 16 anecdotes as topic/ (4585)
 - 17 letter/ (851746)
 - 18 news/ (164223)
 - 19 editorial/ (362955)
 - 20 exp historical article/ (325557)
 - 21 comment/ or case report/ (2283007)
 - 22 (letter or comment\$).ti. (98260)
 - 23 or/16-22 (3389340)
 - 24 23 not (randomized controlled trial/ or randomized controlled trial as topic/ or random\$).ti,ab. (3376109)
 - 25 exp animal model/ (424361)
 - 26 exp rodentia/ (2706249)
 - 27 exp animal experimentation/ (6453)
 - 28 exp animals, laboratory/ (735840)
 - 29 exp animals/ not humans/ (3993592)
 - 30 (rat or rats or monkey\$ or rodent\$ or dog or dogs or cat or cats or feline or canine or primate\$ or macaque\$ or mouse or mice).ti. (1401317)
 - 31 or/24-30 (7988989)
 - 32 15 not 31 (230104)
 - 33 exp Anti-Retroviral Agents/ (66404)
 - 34 Antiretroviral Therapy, Highly Active/ (17734)
 - 35 HAART.ti,ab. (10647)
 - 36 (NRTI\$ or NNRTI\$).ti,ab. (4051)
 - 37 ((antiretroviral or anti-retroviral) adj2 (therap\$ or treatment\$ or agent\$ or drug\$)).ti,ab. (38805)
 - 38 ((nucleoside or non-nucleoside) adj1 reverse transcriptase inhibitor\$).ti,ab. (4212)
 - 39 ((protease or HIV integrase) adj1 inhibitor\$).ti,ab. (28039)
 - 40 (didanosine or lamivudine or nevirapine or stavudine or zidovudine or indinavir or nelfinavir or ritonavir or saquinavir or emtricitabine or rilpivirine or lopinavir or amprenavir or fosamprenavir or atazanavir or darunavir or tipranavir or maraviroc or enfuvirtide or raltegravir

- or etravirine or abacavir or tenofovir or efavirenz or Kaletra or Combivir or Truvada or Atripla or Trizivir or Sustiva).ti,ab. (28631)
- 41 (Stribild or eviplera or kivexa or elvitegravir or ziagen or emtriva or epivir or complera or retrovir or viread or stocrin or intelence or viramune or edurant or reyataz or prezista or telzir or norvir or aptivus or celsentri or dolutegravir or tivicaay or vitekta or isentress).ti,ab. (946)
- 42 (Trio or epzicom or zerit or amdoxovir or videx or rescaptor or delavirdine or lersivirine or crixivan or invirase or lexiva or viracept or fuzeon or selzentry or cenicriviroc or ibalizumab).ti,ab. (1007)
- 43 ((anti-HIV or anti-aids) adj1 (drug\$ or agent\$)).ti,ab. (2334)
- 44 or/33-43 (111084)
- 45 (PI adj2 (dual or boosted or therapy or monotherapy or mono-therapy)).ti,ab. (654)
- 46 (salvage adj2 (therap\$ or treatment\$)).ti,ab. (6399)
- 47 44 or 45 or 46 (117069)
- 48 32 and 47 (60455)
- 49 treatment failure/ and exp Anti-Retroviral Agents/ (1410)
- 50 Drug Resistance/ and exp Anti-Retroviral Agents/ (519)
- 51 exp Drug Resistance, Viral/ (10675)
- 52 ((multidrug or multi-drug) adj2 (resistant or resistance or failure)).ti. (12213)
- 53 (virologic\$ adj2 (resistant or resistance or failure)).ti,ab. (2290)
- 54 treatment failure.ti. (1197)
- 55 ((antiretroviral\$ or anti-retroviral\$ or PI or protease inhibitor\$ or NNRTI) adj2 (resistant or resistance or failure)).ti,ab. (3069)
- 56 (viral load adj2 blip\$).ti,ab. (19)
- 57 M184V.ti,ab. (717)
- 58 ((didanosine or lamivudine or nevirapine or stavudine or zidovudine or indinavir or nelfinavir or ritonavir or saquinavir or emtricitabine or rilpivirine or lopinavir or amprenavir or fosamprenavir or atazanavir or darunavir or tipranavir or maraviroc or enfuvirtide or raltegravir or etravirine or abacavir or tenofovir or efavirenz or Kaletra or Combivir or Truvada or Atripla or Trizivir or Sustiva or Stribild or eviplera or kivexa or elvitegravir or ziagen or emtriva or epivir or complera or retrovir or viread or stocrin or intelence or viramune or edurant or reyataz or prezista or telzir or norvir or aptivus or celsentri or dolutegravir or tivicaay or vitekta or isentress or Trio or epzicom or zerit or amdoxovir or videx or rescaptor or delavirdine or lersivirine or crixivan or invirase or lexiva or viracept or fuzeon or selzentry or cenicriviroc or ibalizumab) adj2 (resistant or resistance or fail\$)).ti,ab. (3133)
- 59 or/49-58 (28632)
- 60 48 and 59 (8680)
- 61 systematic review/ (0)
- 62 meta-analysis/ (50850)
- 63 meta-analysis as topic/ (13984)
- 64 (meta-analy\$ or metanaly\$ or metaanaly\$ or meta analy\$ or meta regression).ti,ab. (69019)
- 65 ((systematic\$ or evidence) adj2 (review\$ or overview\$)).ti,ab. (79601)
- 66 (reference list\$ or bibliograph\$ or hand search\$ or manual search\$ or relevant journals).ab. (26836)
- 67 (search strategy or search criteria or systematic search or study selection or data extraction).ab. (28760)
- 68 (search\$ adj4 literature).ti,ab. (29652)
- 69 (medline or pubmed or cochrane or psychlitt or psychlit or psychinfo or cinahl or science citation index or bids or cancerlit).ab. (85742)
- 70 cochrane.jw. (11336)
- 71 ((multiple treatment\$ or indirect or mixed) adj2 comparison\$).ti,ab. (1444)
- 72 or/61-71 (208234)

- 73 randomized controlled trial.pt. (385506)
- 74 controlled clinical trial.pt. (89648)
- 75 randomi#ed.ti,ab. (390813)
- 76 placebo.ab. (158461)
- 77 randomly.ab. (219847)
- 78 clinical trials as topic.sh. (171958)
- 79 trial.ti. (131696)
- 80 or/73-79 (954672)
- 81 epidemiologic studies/ (6058)
- 82 exp case control studies/ (682007)
- 83 exp cohort studies/ (1387291)
- 84 cross-sectional studies/ (182937)
- 85 case control.ti,ab. (80826)
- 86 (cohort adj (study or studies or analys\$)).ti,ab. (95974)
- 87 ((follow up or observational or uncontrolled or non randomi#ed) adj (study or studies)).ti,ab. (89396)
- 88 ((longitudinal or retrospective or prospective) and (study or studies or review or analys\$ or cohort\$)).ti,ab. (682927)
- 89 cross sectional.ti,ab. (179052)
- 90 or/81-89 (2005715)
- 91 Multicenter Study/ (178984)
- 92 exp risk/ (852722)
- 93 odds ratio/ (61784)
- 94 exp survival analysis/ (190238)
- 95 or/91-94 (1142738)
- 96 72 or 80 or 90 or 95 (3404233)
- 97 60 and 96 (3491)
- 98 limit 97 to english language (3322)
- 99 (201109\$ or 201110\$ or 201111\$ or 201112\$ or 2012\$ or 2013\$ or 2014\$).ed. (2930624)
- 100 98 and 99 (760)

BHIVA ART Guideline: 2014 update SEARCH PROTOCOL: main databases search

Search 5: ART in HIV patients with AIDS associated neurocognitive impairment or non-aids related comorbidities (CKD, CVD, bone diseases eg osteoporosis, osteopenia, psychiatric illness, hyperlipidaemia)

Covers questions 14 and 15

Component	Description
Review area	ART use in HIV patients with AIDS associated neurocognitive impairment or non-aids related comorbidities (CKD ,CVD bone diseases eg osteoporosis, osteopenia, psychiatric, hyperlipidaemia)
Objectives	To establish whether certain treatments should be avoided in patients with specified non aids comorbidities and/or certain treatments selected for better outcomes in HIV related cormorbidities
Populations	HIV infected on HAART Adults – all questions
Interventions	All drugs
Comparisons/ aspects covered by search	Risk of each/ all drugs
Outcomes	To be decided by writing groups
Study designs	SRs, RCTs, observational, risk
Exclusions	Animal studies, letters, editorials, comments, case reports, Non English studies.
How the information was searched	Databases: Medline, Embase, Cochrane Library Language: restrict to English only date parameters : September 2011-current
Search terms and date searched	HIV + ARVS + comorbs See attached strategy document for details: searched 8 August 2014
Search results	Medline/premedline= 937 Embase= 1450 Cochrane = 104 Total=2491 Total deduplicated/title sifted = 1685
The review strategy (The methods that will be used to review the evidence, outlining exceptions and subgroups.)	

Database: Ovid MEDLINE(R) Daily Update <August 07, 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

-
- 1 exp HIV/ (85366)
 - 2 exp HIV Infections/ (236083)
 - 3 HIV Long-Term Survivors/ (591)
 - 4 AIDS Serodiagnosis/ (6152)
 - 5 (aids adj3 virus).ti,ab. (1910)
 - 6 (HIV or HIV1 or HIV2 or hiv-1 or hiv-2).ti,ab. (236950)
 - 7 (human immunodeficiency virus or human immunodeficiency virus or human immunodeficiency virus or human immune-deficiency virus).ti,ab. (71949)
 - 8 (human immun\$ adj3 deficiency virus).ti,ab. (465)
 - 9 (acquired immunodeficiency syndrome or acquired immunodeficiency syndrome or acquired immuno-deficiency syndrome or acquired immune-deficiency syndrome).ti,ab. (19856)
 - 10 (acquired immun\$ adj3 deficiency syndrome).ti,ab. (5197)
 - 11 or/1-10 (324227)
 - 12 exp child/ or exp infant/ or (child\$ or neonat\$ or infant\$).ti. (2168961)
 - 13 exp Adult/ or adult\$.ti. (5734670)
 - 14 12 not 13 (1479988)
 - 15 11 not 14 (307079)
 - 16 anecdotes as topic/ (4585)
 - 17 letter/ (851907)
 - 18 news/ (164287)
 - 19 editorial/ (363061)
 - 20 exp historical article/ (325570)
 - 21 comment/ or case report/ (2283455)
 - 22 (letter or comment\$).ti. (98289)
 - 23 or/16-22 (3389982)
 - 24 23 not (randomized controlled trial/ or randomized controlled trial as topic/ or random\$).ti,ab. (3376748)
 - 25 exp animal model/ (424409)
 - 26 exp rodentia/ (2706387)
 - 27 exp animal experimentation/ (6453)
 - 28 exp animals, laboratory/ (735876)
 - 29 exp animals/ not humans/ (3993766)
 - 30 (rat or rats or monkey\$ or rodent\$ or dog or dogs or cat or cats or feline or canine or primate\$ or macaque\$ or mouse or mice).ti. (1401486)
 - 31 or/24-30 (7989962)
 - 32 15 not 31 (230164)
 - 33 exp Anti-Retroviral Agents/ (66410)
 - 34 Antiretroviral Therapy, Highly Active/ (17734)
 - 35 HAART.ti,ab. (10648)
 - 36 (NRTI\$ or NNRTI\$).ti,ab. (4052)
 - 37 ((antiretroviral or anti-retroviral) adj2 (therap\$ or treatment\$ or agent\$ or drug\$)).ti,ab. (38826)
 - 38 ((nucleoside or non-nucleoside) adj1 reverse transcriptase inhibitor\$).ti,ab. (4212)
 - 39 ((protease or HIV integrase) adj1 inhibitor\$).ti,ab. (28039)
 - 40 (didanosine or lamivudine or nevirapine or stavudine or zidovudine or indinavir or nelfinavir or ritonavir or saquinavir or emtricitabine or rilpivirine or lopinavir or amprenavir or fosamprenavir or atazanavir or darunavir or tipranavir or maraviroc or enfuvirtide or raltegravir

or etravirine or abacavir or tenofovir or efavirenz or Kaletra or Combivir or Truvada or Atripla or Trizivir or Sustiva).ti,ab. (28635)

41 (Stribild or eviopera or kivexa or elvitegravir or ziagen or emtriva or epivir or complera or retrovir or viread or stocrin or intelence or viramune or edurant or reyataz or prezista or telzir or norvir or aptivus or celsentri or dolutegravir or tivicaay or vitekta or isentress).ti,ab. (946)

42 (Trii or epzicom or zerit or amdoxovir or videx or rescriptor or delavirdine or lersivirine or crixivan or invirase or lexiva or viracept or fuzeon or selzentry or cenicriviroc or ibalizumab).ti,ab. (1007)

43 ((anti-HIV or anti-aids) adj1 (drug\$ or agent\$)).ti,ab. (2334)

44 or/33-43 (111112)

45 32 and 44 (60438)

46 Cognition Disorders/ (51807)

47 AIDS Dementia Complex/ (3412)

48 Toxoplasmosis, Cerebral/ (1104)

49 Meningitis, Cryptococcal/ (1404)

50 Leukoencephalopathy, Progressive Multifocal/ (2415)

51 (HAND adj1 HIV).ti,ab. (42)

52 (dementia or toxoplasmosis or leukoencephalopath\$ or meningitis).ti,ab. (125533)

53 ((neuro\$ or cognition or cognitive or NP) adj3 (defect\$ or impairment or disorder\$ or dysfunction\$)).ti,ab. (129800)

54 or/46-53 (270826)

55 aids-associated nephropathy/ or exp renal insufficiency/ (127012)

56 Kidney/de [Drug Effects] (37010)

57 exp Cardiovascular Diseases/ (1896395)

58 bone diseases, metabolic/ or exp osteoporosis/ (49426)

59 exp "Bone and Bones"/de [Drug Effects] (16164)

60 exp Hyperlipidemias/ (56671)

61 mental disorders/ or exp delirium, dementia, amnestic, cognitive disorders/ (302491)

62 ((neph\$ or kidney or renal or cardio\$ or myocardial or heart or bone or psychiatric or lipid) adj2 (disorder\$ or disease\$ or dysfunction or comorb\$ or co-morb\$)).ti,ab. (386206)

63 (heart attack\$ or myocardial infarct\$).ti,ab. (151458)

64 (hyperlip?emia\$ or osteoporos\$ or osteop?enia\$).ti,ab. (52594)

65 ((neph\$ or renal or kidney) adj2 (injury or failure)).ti,ab. (94860)

66 or/55-65 (2596142)

67 45 and 54 (1912)

68 45 and 66 (4190)

69 67 or 68 (5108)

70 systematic review/ (0)

71 meta-analysis/ (50864)

72 meta-analysis as topic/ (13985)

73 (meta-analy\$ or metanaly\$ or metaanaly\$ or meta analy\$ or meta regression).ti,ab. (69073)

74 ((systematic\$ or evidence) adj2 (review\$ or overview\$)).ti,ab. (79662)

75 (reference list\$ or bibliograph\$ or hand search\$ or manual search\$ or relevant journals).ab. (26849)

76 (search strategy or search criteria or systematic search or study selection or data extraction).ab. (28773)

77 (search\$ adj4 literature).ti,ab. (29670)

78 (medline or pubmed or cochrane or psychlitt or psychlit or psychinfo or cinahl or science citation index or bids or cancerlit).ab. (85803)

79 cochrane.jw. (11336)

80 ((multiple treatment\$ or indirect or mixed) adj2 comparison\$).ti,ab. (1444)

- 81 or/70-80 (208354)
- 82 randomized controlled trial.pt. (385531)
- 83 controlled clinical trial.pt. (89651)
- 84 randomi#ed.ti,ab. (390943)
- 85 placebo.ab. (158500)
- 86 randomly.ab. (219923)
- 87 clinical trials as topic.sh. (171967)
- 88 trial.ti. (131750)
- 89 or/82-88 (954899)
- 90 epidemiologic studies/ (6059)
- 91 exp case control studies/ (682085)
- 92 exp cohort studies/ (1387412)
- 93 cross-sectional studies/ (182963)
- 94 case control.ti,ab. (80846)
- 95 (cohort adj (study or studies or analys\$)).ti,ab. (96024)
- 96 ((follow up or observational or uncontrolled or non randomi#ed) adj (study or studies)).ti,ab. (89446)
- 97 ((longitudinal or retrospective or prospective) and (study or studies or review or analys\$ or cohort\$)).ti,ab. (683210)
- 98 cross sectional.ti,ab. (179143)
- 99 or/90-98 (2006200)
- 100 Multicenter Study/ (179002)
- 101 exp risk/ (852781)
- 102 odds ratio/ (61790)
- 103 exp survival analysis/ (190242)
- 104 or/100-103 (1142819)
- 105 81 or 89 or 99 or 104 (3405010)
- 106 69 and 105 (3035)
- 107 (201109\$ or 201110\$ or 201111\$ or 201112\$ or 2012\$ or 2013\$ or 2014\$).ed. (2933093)
- 108 106 and 107 (973)
- 109 limit 108 to english language (937)