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/µL, 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/µL? 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/µL

**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, grade 3/4 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, Grade 3/4 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

<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review area</td>
<td><strong>Timing of ART initiation</strong></td>
</tr>
<tr>
<td>Objectives</td>
<td>To assess the benefits and risks of earlier rather than later initiation of ART</td>
</tr>
<tr>
<td>Populations</td>
<td>Chronic HIV Infection, Primary HIV infection, Advanced HIV disease, HIV infected with HIV negative partner (sero-discordance)</td>
</tr>
<tr>
<td>Interventions</td>
<td>Antiretroviral therapy (all drugs), HAART</td>
</tr>
<tr>
<td>Comparisons/aspects covered by search</td>
<td>Initiation: at diagnosis: at CD4 count &gt;350: at CD4 count &gt;500</td>
</tr>
<tr>
<td>Outcomes</td>
<td>To be decided by writing groups</td>
</tr>
<tr>
<td>Study designs</td>
<td>SRs, RCTs, observational studies, risk, economic</td>
</tr>
<tr>
<td>Exclusions</td>
<td>Animal studies, letters, editorials, comments, case reports, Non English studies.</td>
</tr>
<tr>
<td>How the information was searched</td>
<td>Databases: Medline, Embase, Cochrane Library</td>
</tr>
<tr>
<td></td>
<td>Language: restrict to English only</td>
</tr>
<tr>
<td></td>
<td>date parameters: database entry date September 2011-current</td>
</tr>
<tr>
<td>Search terms and date searched</td>
<td>HIV + ARVS + early/later starting</td>
</tr>
<tr>
<td></td>
<td>See attached Medline strategy document for details: searched 6 August 2014</td>
</tr>
<tr>
<td>Search results</td>
<td>Medline/premedline= 619\n Embase= 756\n Cochrane = 150\n Total= 1525\n Total deduplicated/title sifted = 798</td>
</tr>
<tr>
<td>The review strategy</td>
<td>To be decided by writing groups</td>
</tr>
<tr>
<td>Key papers</td>
<td></td>
</tr>
</tbody>
</table>

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 immuno-deficiency virus or human immune-deficiency virus).ti,ab. (71696)
8. (human immuno$ 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 Ant-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 tenovir or efavirenz or Kaletra or Combivir or Truvada or Atripla or Trizivir or Sustiva).ti,ab. (28504)

Search 1 : When to Initiate ART
Search 1 : When to Initiate ART

41 (Stribild or eviplera or kivexa or elvitegravir or ziagen or emtriva or epivir or complera or retrovir or viread or stocrin or intence or viramune or edurant or reyataz or prezista or telzir or norvir or aptivus or celsentri or dolutegravir or tivicay or viteka 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$)).ti,ab. (2335)
44 or/33-43 (110614)
45 32 and 44 (60120)
46 ((early or earlier or immediat$ 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 rilpirivine or lopinavir or amprenavir or fosamprenavir or atazanavir or darunavir or tipranavir or maraviroc or enfuvirtide 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 intence or viramune or edurant or reyataz or prezista or telzir or norvir or aptivus or celsentri or dolutegravir or tivicay or viteka 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. (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 cohrane or psychlit or psyclit 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)
Search 1: When to Initiate ART

4 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 utili$ 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*

<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Review area</strong></td>
<td>Preferred initial ART regimens</td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
<td>Safety and efficacy of various different firstline regimens in ART naïve patients including choice of third agent</td>
</tr>
<tr>
<td><strong>Populations</strong></td>
<td>HIV infected, naïve to ART</td>
</tr>
<tr>
<td></td>
<td>Adults – all questions</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>All ARVS includes</td>
</tr>
<tr>
<td></td>
<td>Fixed dose combinations, PI monotherapy, PI based dual therapy, NRTI sparing regimens</td>
</tr>
<tr>
<td><strong>Comparisons/ aspects covered by search</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>To be decided by writing groups</td>
</tr>
<tr>
<td><strong>Study designs</strong></td>
<td>SRs, RCTs,</td>
</tr>
<tr>
<td><strong>Exclusions</strong></td>
<td>Animal studies, letters, editorials, comments, case reports Non English studies.</td>
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<tr>
<td><strong>How the information was searched</strong></td>
<td>Databases: Medline, Embase, Cochrane Library</td>
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<td>Language: restrict to English only</td>
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<td>date parameters: September 2011 to current</td>
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<td><strong>Search terms and date searched</strong></td>
<td>HIV + ARVS + naïve/ firstline</td>
</tr>
<tr>
<td></td>
<td>See attached strategy document for details: searched 6 August 2014</td>
</tr>
<tr>
<td><strong>Search results</strong></td>
<td>Medline/premedline= 451</td>
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<tr>
<td></td>
<td>Embase= 579</td>
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<td>Cochrane = 360</td>
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<td>Total=1390</td>
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<td></td>
<td>Total deduplicated/title sifted = 720</td>
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<tr>
<td><strong>The review strategy</strong></td>
<td>(The methods that will be used to review the evidence, outlining exceptions and subgroups.)</td>
</tr>
<tr>
<td><strong>Key papers</strong></td>
<td></td>
</tr>
</tbody>
</table>
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1. exp HIV/ (85063)
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8. (human immu$ adj3 deficiency virus).ti,ab. (463)
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10. (acquired immu$ 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)
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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)
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31. or/24-30 (7959228)
32. 15 not 31 (229126)
33. exp Anti-Retroviral Agents/ (66115)
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$).ti,ab. (27937)
40. (didanosine or lamivudine or nevirapine or stavudine or zidovudine or indinavir or nelfinavir or ritonavir or saquinavir or emtricitabine or rilpirivine or lopinavir or amprenavir or fosamprenavir or atazanavir or darunavir or tipranavir or maraviroc or enfuvirtide or raltegravir
or etravirine or abacavir or tenofovir or efavirenz or Kaletra or Combivir or Truvada or Atripla or Trizivir or Sustiva).ti,ab. (28504)
41 (Stridbild or eviplera or kivexa or elvitegravir or ziagen or emtriva or epivir or complera or retrovir or viread or stocrin or intenence or viramune or edurant or reyataz or prezista or telzir or norvir or apitivus or celsentri or dolutegravir or tivicay or vitekta or isentress).ti,ab. (944)
42 (Trii or epzicom or zerit or amdoxovir or videx or rescriptor or delavirdine or lersivirine or crixivan or invirase or lexiva or viracept or fuzeon or selzentry or cenicriviroc or ibalizumab).ti,ab. (1006)
43 ((anti-HIV or anti-aids) adj1 (drug$ 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$)).ti,ab. (78764)
57 (reference list$ or bibliograph$ or hand search$ or manual search$ or relevant journals).ab. (2629)
58 (search strategy or search criteria or systematic search or study selection or data extraction).ab. (28200)
59 (search$ adj4 literature).ti,ab. (29347)
60 (medline or pubmed or cohrane or psychlitt or psyclit or psychinfo or cinahl or science citation index or bids or cancerlit).ab. (84573)
61 cochrane.jw. (11109)
62 ((multiple treatment$ or indirect or mixed) adj2 comparison$).ti,ab. (1441)
63 or/52-62 (206294)
64 randomized controlled trial.pt. (380240)
65 controlled clinical trial.pt. (88960)
66 randomi#ed.ti,ab. (385723)
67 placebo.ab. (156778)
68 randomly.ab. (217817)
69 clinical trials as topic.sh. (171327)
70 trial.ti. (129810)
71 or/64-70 (946010)
72 63 or 71 (1093791)
73 51 and 72 (1947)
74 limit 73 to english language (1879)
75 (201109$ or 201110$ or 201111$ or 201112$ or 2012$ or 2013$ or 2014$).ed. (2902617)
76 74 and 75 (451)
Search 3: Switching/simplification of ART regimens

Covers Section 3 Questions 10 and 11

<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
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<tbody>
<tr>
<td>Review area</td>
<td>ART simplification/ switching options</td>
</tr>
<tr>
<td>Objectives</td>
<td>Safety and efficacy of switching drug therapy or simplifying drug regimens</td>
</tr>
<tr>
<td>Populations</td>
<td>HIV infected on HAART</td>
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<tr>
<td></td>
<td>Adults – all questions</td>
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<tr>
<td>Interventions</td>
<td>All ARVS including PI monotherapy, alternative NRTI backbone, alternative third agents</td>
</tr>
<tr>
<td>Comparisons/ aspects covered by search</td>
<td>conventional HAART</td>
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<tr>
<td>Outcomes</td>
<td>To be decided by writing groups</td>
</tr>
<tr>
<td>Study designs</td>
<td>SRs, RCTs</td>
</tr>
<tr>
<td>Exclusions</td>
<td>Animal studies, letters, editorials, comments, case reports, Non English studies.</td>
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<td>How the information was searched</td>
<td>Databases: Medline, Embase, Cochrane Library</td>
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<td>Search terms and date searched</td>
<td>HIV + ARVS + switching/ simplification</td>
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The review strategy (The methods that will be used to review the evidence, outlining exceptions and subgroups.)

Key papers
BHIVA Treatment Guidelines: literature search strategies

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 immunedeficiency virus or human immuno-deficiency virus or human immune-deficiency virus).ti,ab. (71696)
8. (human immun$ adj3 deficiency virus).ti,ab. (463)
9. (acquired immunodeficiency syndrome or acquired immunedeficiency 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/ (661115)
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

Search 3: Switching/simplification of ART regimens
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 intence or viramune or edurant or reyataz or prezista or telzir or norvir or aptvus or celsentri or dolutegravir or tivicay or viteka 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 anti retroviral$ 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$) adj2 (didanosine or lamivudine or nevirapine or stavudine or zidovudine or indinavir or nelfinavir or ritonavir or saquinavir or emtricitabine or rilpirivine or lopinavir or ampenavir or fosamprenavir or atazanavir or darunavir or tipranavir or maraviroc or enfuvirtide or raltegravir or etravirine or abacavir or tenofovir or efavirenz or Kaletra or Combivir or Truvada or Atripla or Trizivir or Sustiva or Stribild or eviplera or kivexa or elvitegravir or ziaen or emtriva or epivir or complera or retrovir or viread or stocrin or intence or viramune or edurant or reyataz or prezista or telzir or norvir or aptvus or celsentri or dolutegravir or tivicay or viteka or isentress or Trii or epzicom or zerit or amdoxovir or videx or rescriptor or delavirdine or lersivirine or crixivan or invirase or lexiva or viracept or fuzeon or selzentry or cenicriviroc or ibalizumab)).ti,ab. (969)
49 (maintenance adj3 (mono-therapy or therapy or regim$ 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 psyclit 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)
Search 4: Virological failure

*Covers Questions 12 and 13*

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<td>Risk of and management of patient with virological failure/ resistance</td>
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<td>Populations</td>
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<td>Interventions</td>
<td>All ARVS, salvage therapy</td>
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<td>Outcomes</td>
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<td>Study designs</td>
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<td>(The methods that will be used to review the evidence, outlining exceptions</td>
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<td>and subgroups.)</td>
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<td>Key papers</td>
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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)
9. (acquired immunodeficiency syndrome or acquired immunodeficiency syndrome or acquired immuno-deficiency syndrome or acquired immune-deficiency syndrome).ti,ab. (19850)
10. (acquired imm$ 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$).ti. (98260)
23. or/16-22 (3389340)
24. 23 not (randomized controlled trial/ or randomized controlled trial as to pic/ or random$).ti,ab. (3376109)
25. exp animal model/ (424361)
26. exp rodential/ (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 (7989899)
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 ...
BHIVA Treatment Guidelines: literature search strategies

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 intelecte or viramune or edurant or reyataz or prezista or telzir or norvir or aptivus or celsentri or dolutegravir or tivicay or vitaekta or isentress).ti,ab. (946)
42 (Trii or epzicom or zerit or amdoxovir or videx or rescriptor or delavirdine or lersivirine or crixivan or inivirase or lexima 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$).ti,ab. (19)
57 M184V.ti,ab. (717)
58 ((didanosine or lamivudine or nevirapine or stavudine or zidovudine or indinavir or nelfinavir or ritonavir or saquinavir or emtricitabine or rilpirivine or dolutegravir or etravirine or abacavir or tenofovir or efavirenz or piv312133)
59 or/49-58 (28632)
60 48 and 59 (8680)
61 systematic review/ (0)
62 meta-analysis/ (50850)
63 meta-analysis as topic/ (13984)
64 (meta-analy$ 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 psychlit or psyclit 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)
Search 4: Virological failure

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)
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

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<th>Component</th>
<th>Description</th>
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<tr>
<td><strong>Review area</strong></td>
<td>ART use in HIV patients with AIDS associated neurocognitive impairment or non-aids related comorbidities (CKD, CVD bone diseases eg osteoporosis, osteopenia, psychiatric, hyperlipidaemia)</td>
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<tr>
<td><strong>Objectives</strong></td>
<td>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 comorbidities</td>
</tr>
<tr>
<td><strong>Populations</strong></td>
<td>HIV infected on HAART&lt;br&gt;Adults – all questions</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>All drugs</td>
</tr>
<tr>
<td><strong>Comparisons/aspects</strong></td>
<td>Risk of each/ all drugs</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>To be decided by writing groups</td>
</tr>
<tr>
<td><strong>Study designs</strong></td>
<td>SRs, RCTs, observational, risk</td>
</tr>
<tr>
<td><strong>Exclusions</strong></td>
<td>Animal studies, letters, editorials, comments, case reports, Non English studies.</td>
</tr>
<tr>
<td><strong>How the information was searched</strong></td>
<td>Databases: Medline, Embase, Cochrane Library&lt;br&gt;Language: restrict to English only&lt;br&gt;date parameters : September 2011-current</td>
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<tr>
<td><strong>Search terms and date searched</strong></td>
<td>HIV + ARVS + comorbs&lt;br&gt;See attached strategy document for details: searched 8 August 2014</td>
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<td><strong>Search results</strong></td>
<td>Medline/premedline= 937&lt;br&gt;Embase= 1450&lt;br&gt;Cochrane = 104&lt;br&gt;Total=2491&lt;br&gt;Total deduplicated/title sifted = 1685</td>
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**The review strategy**<br>(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 immunodeficiency virus).ti,ab. (71949)
8. (human immun$ adj3 deficiency virus).ti,ab. (465)
9. (acquired immunodeficiency syndrome or acquired immunodeficiency syndrome or acquired immunodeficiency syndrome or acquired immunodeficiency 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$).ti,ab. (28039)
40. (didanosine or lamivudine or nevirapine or stavudine or zidovudine or indinavir or nelfinavir or ritonavir or saquinavir or emtricitabine or rilpivirine or lopinavir or amprenavir or fosamprenavir or atazanavir or darunavir or tipranavir or maraviroc or enfuvirtide or raltegravir
or etravirine or abacavir or tenofovir or efavirenz or Kaletra or Combivir or Truvada or Atripla or Trizivir or Sustiva).ti,ab. (28635)
41 (Stribild or eviplera or kivexa or elvitegravir or zidovudine or emtriva or epivir or compilera or retrovir or viread or stocrin or intenelle or viramune or edurant or reyataz or prezista or telzir or norvir or apvus or celsentri or dolutegravir or tivicay or viread or crixivan or invirase or lexiva or viracept or fuzeon or selzentry or cenicriviroc or ibalizumab).ti,ab. (1007)
42 (Trii or epzicom or zerit or amdoxovir or videx or rescriptor or delavirdine or lersivirine or crixivan or invirase or lexicor or viread or stocrin or intelence or viramune or edurant or reyataz or prezista or telzir or norvir or apvus or celsentri or dolutegravir or tivicay or viread or crixivan or invirase or lexiva or viracept or fuzeon or selzentry or cenicriviroc or ibalizumab).ti,ab. (1007)
43 ((anti-HIV or anti-aids) adj1 (drug$ or agent$)).ti,ab. (2334)
44 or/33-43 (111112)
45 32 and 44 (60438)
46 Cognition Disorders/ (51807)
47 AIDS Dementia Complex/ (3412)
48 Toxoplasmosis, Cerebral/ (1104)
49 Meningitis, Cryptococcal/ (1404)
50 Leukoencephalopathy, Progressive Multifocal/ (2415)
51 (HAND adj1 HIV).ti,ab. (42)
52 (dementia or toxoplasmosis or leukoencephalopathy$ or meningitis).ti,ab. (125533)
53 ((neuro$ or cognition or cognitive or NP) adj3 (defect$ or impairment or disorder$ or dysfunction$)).ti,ab. (129800)
54 or/46-53 (270826)
55 aids-associated nephropathy/ or exp renal insufficiency/ (127012)
56 Kidney/de [Drug Effects] (37010)
57 exp Cardiovascular Diseases/ (1896395)
58 bone diseases, metabolic/ or exp osteoporosis/ (49426)
59 exp "Bone and Bones"/de [Drug Effects] (16164)
60 exp Hyperlipidemias/ (56671)
61 mental disorders/ or exp delirium, dementia, amnestic, cognitive disorders/ (302491)
62 ((neph$r$ 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$r$ or renal or kidney) adj2 (injury or failure)).ti,ab. (94860)
66 or/55-66 (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-analysis$ or metanalysis$ 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 psychlit or psycliit 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)