

Appendix 2. PICO questions and literature search strategies

1 What to start

Preferred regimen/choice of third agent

Population: People living with HIV, naïve to antiretroviral therapy (ART)

Intervention: Triple ART based on efavirenz, darunavir/r or atazanavir/r, raltegravir, rilpivirine, elvitegravir/cobicistat and dolutegravir-containing combination ART (2015/2016 recommended agents)

Comparator: Other 2015/2016 recommended third agents: doravirine, bictegravir, dolutegravir/lamivudine, boosted-atazanavir/lamivudine and boosted darunavir/lamivudine

Outcome: Virological suppression (viral load <50 copies/mL), virological failure, discontinuing regimen secondary to adverse events (or for any reason), grade 3/4 adverse events, emergent HIV drug resistance and patient-reported outcomes

Question: What is the preferred first-line regimen/choice of third agent for people living with HIV?

Search: Medline, Embase and Cochrane Library: January 2014 to March 2021

Medline and Embase limited also to English only, adults, humans and type of study (randomised controlled trials, systematic reviews and observational studies)

ProQuest® Medline

Set#	Searched for	Results
S1	(MESH.EXACT("AIDS Serodiagnosis") OR MESH.EXACT.EXPLODE("HIV Infections") OR MESH.EXACT.EXPLODE("HIV") OR MESH.EXACT("HIV Long-Term Survivors"))	306166
S2	(ti,ab(HIV or HIV1 or HIV2 or "human immun* deficien[*3]" or PLWH or AIDS near/3 virus or "acquired immun* deficien[*3]"))	302032
S3	(ti,ab("human immunodeficiency virus" or "human immunodeficiency virus" or "human immunodeficiency virus" or "human immune-deficiency virus"))	83808
S4	(ti,ab("acquired immunodeficiency syndrome" or "acquired immunodeficiency syndrome" or "acquired immunodeficiency syndrome" or "acquired immune-deficiency syndrome"))	21328
S5	S4 OR S3 OR S2 OR S1	390019
S6	(MESH.EXACT.EXPLODE("Anti-Retroviral Agents"))	79327

S7	(MESH.EXACT("Antiretroviral Therapy, Highly Active"))	20403
S8	ti,ab(HAART)	11660
S9	(ti,ab((antiretroviral or anti-retroviral) near/3 (therap* or treat* or agent* or drug* or medication* or regime*)))	55573
S10	(ti,ab(NRTI* or NNRTI*))	4851
S11	(ti,ab((nucleoside or non-nucleoside or nonnucleoside) near/2 "reverse transcriptase inhibitor*"))	6413
S12	(ti,ab((protease or integrase) near/1 inhibitor*))	33834
S13	(ti,ab((anti-HIV or anti-aids) near/1 (drug* or agent* or therap* or treat* or agent* or regime*)))	3994
S14	S13 OR S12 OR S11 OR S10 OR S9 OR S8 OR S7 OR S6	134481
S15	(ti,ab(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))	34037
S16	(ti,ab(Stribild or eviplera or kivexa or elvitegravir or ziagen or emtriva or epivir or complexa 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))	1849
S17	(ti,ab(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))	983
S18	(ti,ab(Biktarvy or cictegravir or tenofovir alafenamide or doravirine or Pifeltro or Delstrigo or Descovy or cabotegravir))	426
S19	S18 OR S17 OR S16 OR S15	34928
S20	S19 OR S14	139480
S21	(ti,ab((firstline or first-line or initial or start* or begin*) near/2 (therap* or regim* or anti-retroviral* or antiretroviral* or agent* or drug* or HAART or ART or treat* or medication*)))	168677
S22	ti,ab(naïve)	78454
S23	S22 OR S21	243160
S24	S20 AND S5	102028
S25	S24 AND S23	13750
S26	(s25) and (la.exact("English"))	13130
S27	(s25) and (pd(>20131231)) and (la.exact("English"))	3674

S28	(S27 and human(yes))	2627
S29	(S27 not (human(yes) or animal(yes)))	1030
S30	S29 OR S28	3655
S31	((MESH.EXACT.EXPLODE("Child") OR MESH.EXACT.EXPLODE("Infant") OR ti,ab(child* or neonat* or infant*)) and (pd(>20131231)) and (la.exact("English"))	438044
S32	((MESH.EXACT.EXPLODE("Adult") OR ti,ab(adult*)) and (pd(>20131231)) and (la.exact("English"))	1231988
S33	((S31 NOT S32)) and (pd(>20131231)) and (la.exact("English"))	288147
S34	((S30 NOT S33)) and (pd(>20131231)) and (la.exact("English"))	3316
S35	((MESH.EXACT("Randomized Controlled Trials as Topic")) and (pd(>20131231)) and (la.exact("English"))	27188
S36	((MESH.EXACT("Random Allocation")) and (pd(>20131231)) and (la.exact("English"))	15376
S37	((MESH.EXACT("Double Blind Method")) and (pd(>20131231)) and (la.exact("English"))	22036
S38	((MESH.EXACT("Single Blind Method")) and (pd(>20131231)) and (la.exact("English"))	6523
S39	((Rtype.exact("clinical trial, phase i")) and (pd(>20131231)) and (la.exact("English"))	4320
S40	((Rtype.exact("clinical trial, phase ii")) and (pd(>20131231)) and (la.exact("English"))	6987
S41	((Rtype.exact("clinical trial, phase iii")) and (pd(>20131231)) and (la.exact("English"))	5489
S42	((Rtype.exact("clinical trial, phase iv")) and (pd(>20131231)) and (la.exact("English"))	677
S43	((Rtype.exact("controlled clinical trial")) and (pd(>20131231)) and (la.exact("English"))	3496
S44	((Rtype.exact("randomized controlled trial")) and (pd(>20131231)) and (la.exact("English"))	89410
S45	((Rtype.exact("multicenter study")) and (pd(>20131231)) and (la.exact("English"))	68681
S46	((Rtype.exact("clinical trial")) and (pd(>20131231)) and (la.exact("English"))	24306
S47	((MESH.EXACT.EXPLODE("Clinical Trials as Topic")) and (pd(>20131231)) and (la.exact("English"))	45679
S48	((ti,ab(clinical near/1 trial*)) and (pd(>20131231)) and (la.exact("English"))	110513
S49	((ti,ab((singl* or doubl* or treb* or tripl*) near/1 (blind* or mask*))) and (pd(>20131231)) and (la.exact("English"))	32940
S50	(MESH.EXACT("placebos")) and (pd(>20131231)) and (la.exact("English"))	1666
S51	(ti,ab(placebo*)) and (pd(>20131231)) and (la.exact("English"))	42826

S52	((ti,ab("randomly allocated")) and (pd(>20131231)) and (la.exact("English"))	8627
S53	((ti,ab(allocated near/2 random*)) and (pd(>20131231)) and (la.exact("English"))	9346
S54	S53 OR S52 OR S51 OR S50 OR S49 OR S48 OR S47 OR S46 OR S45 OR S44 OR S43 OR S42 OR S41 OR S40 OR S39 OR S38 OR S37 OR S36 OR S35	322441
S55	((MESH.EXACT("Meta-Analysis as Topic")) and (pd(>20131231)) and (la.exact("English"))	2803
S56	((ti,ab("meta analy*")) and (pd(>20131231)) and (la.exact("English"))	80161
S57	(Rtype.EXACT("Meta-Analysis")) and (pd(>20131231)) and (la.exact("English"))	45947
S58	(ti,ab(metaanaly*)) and (pd(>20131231)) and (la.exact("English"))	587
S59	((ti,ab(systematic near/1 (review* or overview*))) and (pd(>20131231)) and (la.exact("English"))	87801
S60	((MESH.EXACT.EXPLODE("Review Literature as Topic")) and (pd(>20131231)) and (la.exact("English"))	3937
S61	((MESH.EXACT("Meta-Analysis as Topic")) and (pd(>20131231)) and (la.exact("English"))	2803
S62	S61 OR S60 OR S59 OR S58 OR S56 OR S55	128582
S63	((MESH.EXACT("Epidemiologic studies")) and (pd(>20131231)) and (la.exact("English"))	1062
S64	((MESH.EXACT.EXPLODE("case control studies")) and (pd(>20131231)) and (la.exact("English"))	68562
S65	((MESH.EXACT.EXPLODE("cohort studies")) and (pd(>20131231)) and (la.exact("English"))	422083
S66	((ti,ab("case control")) and (pd(>20131231)) and (la.exact("English"))	35452
S67	((ti,ab(cohort near/1 (study or studies))) and (pd(>20131231)) and (la.exact("English"))	93664
S68	((ti,ab("Cohort analy*")) and (pd(>20131231)) and (la.exact("English"))	3171
S69	((ti,ab("follow up" near/1 (study or studies))) and (pd(>20131231)) and (la.exact("English"))	11324
S71	((ti,ab(observational near/1 (study or studies))) and (pd(>20131231)) and (la.exact("English"))	52710
S72	(ti,ab(Longitudinal)) and (pd(>20131231)) and (la.exact("English"))	75563
S73	(ti,ab(Retrospective)) and (pd(>20131231)) and (la.exact("English"))	179523
S74	((ti,ab("Cross sectional")) and (pd(>20131231)) and (la.exact("English"))	130134
S75	((MESH.EXACT("Cross-sectional studies")) and (pd(>20131231)) and (la.exact("English"))	98426
S76	S75 OR S74 OR S73 OR S72 OR S71 OR S69 OR S68 OR S67 OR S66 OR S65 OR S64 OR S63	773624
S77	((s34 AND (s54 OR s62 OR s76))) and (pd(>20131231)) and (la.exact("English"))	n=2035

Search results

Medline = 2035; Embase = 3360; Cochrane Library = 542

Total of all three databases – without duplicates/triplicates: n=4542

2 Virological failure/transmitted drug resistance

A Virological failure

No PICO

Questions:

What are the optimal regimens post-non-nucleoside reverse transcriptase inhibitor (NNRTI) failure first line?

What are the optimal regimens post-integrase inhibitor failure first line?

What are the optimal regimens post-protease inhibitor (PI) failure first line?

What is the optimal management of low-level viraemia?

Search: Medline, Embase and Cochrane Library: August 2014 to March 2021

Medline and Embase limited also to English only, adults, humans and type of study (randomised controlled trials, systematic reviews and observational studies)

ProQuest® Medline

Set#	Searched for	Results
S1	(MESH.EXACT.EXPLODE("HIV Infections") OR MESH.EXACT.EXPLODE("HIV") OR MESH.EXACT("HIV Long-Term Survivors"))	312297
S2	(ti,ab(HIV or HIV1 or HIV2 or "human immun* deficien[*3]" or PLWH))	306176
S3	(ti,ab("human immunodeficiency virus" or "human immunodeficiency virus" or "human immunodeficiency virus" or "human immune-deficiency virus"))	85621
S4	(s1 or s2 or s3)	396461
S5	(MESH.EXACT("Salvage Therapy"))	14213
S6	(ti,ab(salvage near/3 (therap* or treatment* or option* or regime* or agent* or setting)))	12545
S7	(ti,ab(switch* near/3 (therap* or treatment* or option* or regime* or agent*)) not ti(suppress*))	8921
S8	(MESH.EXACT("Drug Resistance, Multiple, Viral"))	1045
S9	(ti,ab((resistan* or "cross resistan*" or crossresistan* or fail*) near/3? (multidrug or "multi-drug" or virologic* or viral or antiretroviral* or "anti-retroviral*" or PI or "protease inhibitor*" or NRTI or NNRTI)))	71445
S10	(ti,ab((resistan* or "cross resistan*" or crossresistan*) near/3 (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	3617

	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 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 or Biktarvy or cictegravir or “tenofovir alafenamide” or doravirine or Pifeltro or Delstrigo or Descovy or cabotegravir)))	
S11	MESH.EXACT("Viremia")	8686
S12	(ti,ab("low level" near/3 (viremi* or viraemi*)))	491
S13	(s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12)	112525
S14	(MESH.EXACT.EXPLODE("Anti-HIV Agents") or MESH.EXACT("Reverse Transcriptase Inhibitors") or MESH.EXACT("HIV Protease Inhibitors") or MESH.EXACT("HIV Integrase Inhibitors"))	69483
S15	(ti,ab(NRTI* OR NNRTI* or “reverse transcriptase inhibit*” or “protease inhibit*” or (integrase near/3 inhib*) or INSTI or nucleoside or “non-nucleoside” or nonnucleoside))	70743
S16	(S14 OR S15)	122787
S17	(MESH.EXACT("Mutation") or ti,ab(mutation*))	802955
S18	(S16 AND S17)	12306
S19	(S13 OR S18)	119384
S20	(S4 AND S19)	20015
S21	(s20) and (la.exact("English"))	19115
S22	(s20) and (pd(>20130731)) and (la.exact("English"))	4662
S23	((S22 and human(yes))) and (pd(>20130731)) and (la.exact("English"))	3419
S24	((S22 not (human(yes) or animal(yes)))) and (pd(>20130731)) and (la.exact("English"))	1160
S25	((S23 OR S24)) and (pd(>20130731)) and (la.exact("English"))	4576
S26	((MESH.EXACT.EXPLODE("Child") OR MESH.EXACT.EXPLODE("Infant") OR ti,ab(child* or neonat* or infant*)) and (pd(>20130731)) and (la.exact("English"))	550341
S27	((MESH.EXACT.EXPLODE("Adult") OR ti,ab(adult*)) and (pd(>20130731)) and (la.exact("English"))	1586585
S28	((S26 NOT S27)) and (pd(>20130731)) and (la.exact("English"))	359031
S29	((S25 NOT S28)) and (pd(>20130731)) and (la.exact("English"))	4290
S30	((S25 NOT S29)) and (pd(>20130731)) and (la.exact("English"))	286

S31	((MESH.EXACT("Randomized Controlled Trials as Topic") or MESH.EXACT("Random Allocation") or MESH.EXACT("Double Blind Method") or MESH.EXACT("Single Blind Method"))) and (pd(>20130731)) and (la.exact("English"))	90409
S32	((Rtype.exact("clinical trial, phase i") or Rtype.exact("clinical trial, phase ii") or Rtype.exact("clinical trial, phase iii") or Rtype.exact("clinical trial, phase iv") or Rtype.exact("controlled clinical trial") or Rtype.exact("randomized controlled trial") or Rtype.exact("multicenter study") or Rtype.exact("clinical trial"))) and (pd(>20130731)) and (la.exact("English"))	218076
S33	((MESH.EXACT.EXPLODE("clinical trials as topic") or MESH.EXACT("placebos"))) and (pd(>20130731)) and (la.exact("English"))	61742
S34	((ti,ab(clinical near/1 trial*)) and (pd(>20130731)) and (la.exact("English"))	137739
S35	((ti,ab((singl* or doubl* or treb* or tripl*) near/1 (blind* or mask*))) and (pd(>20130731)) and (la.exact("English"))	40704
S36	((ti,ab(placebo* or "randomly allocated" or (allocated near/2 random*))) and (pd(>20130731)) and (la.exact("English"))	63005
S37	((s31 or s32 or s33 or s34 or s35 or s36)) and (pd(>20130731)) and (la.exact("English"))	411243
S38	((MESH.EXACT("Meta-Analysis as Topic"))) and (pd(>20130731)) and (la.exact("English"))	3682
S39	((ti,ab("meta analy*" or metaanaly*))) and (pd(>20130731)) and (la.exact("English"))	100774
S40	(Rtype.EXACT("Meta-Analysis")) and (pd(>20130731)) and (la.exact("English"))	59389
S41	((ti,ab(systematic near/1 (review* or overview*))) and (pd(>20130731)) and (la.exact("English"))	110394
S42	((MESH.EXACT.EXPLODE("Review Literature as Topic") or MESH.EXACT("Meta-Analysis as Topic"))) and (pd(>20130731)) and (la.exact("English"))	8064
S43	((s38 or s39 or s40 or s41 or s42)) and (pd(>20130731)) and (la.exact("English"))	165719
S44	((MESH.EXACT.EXPLODE("case control studies") or MESH.EXACT("Epidemiologic studies") or MESH.EXACT.EXPLODE("cohort studies"))) and (pd(>20130731)) and (la.exact("English"))	620185
S45	((ti,ab("case control"))) and (pd(>20130731)) and (la.exact("English"))	44145
S46	((ti,ab(cohort near/1 (study or studies)))) and (pd(>20130731)) and (la.exact("English"))	117162
S47	((ti,ab("Cohort analy*"))) and (pd(>20130731)) and (la.exact("English"))	3996
S48	((ti,ab("follow up" near/1 (study or studies)))) and (pd(>20130731)) and (la.exact("English"))	14009
S49	((ti,ab(observational near/1 (study or studies)))) and (pd(>20130731)) and (la.exact("English"))	65908
S50	((ti,ab(Longitudinal or Retrospective or "Cross sectional"))) and (pd(>20130731)) and (la.exact("English"))	460037

S51	((MESH.EXACT("Cross-sectional studies"))) and (pd(>20130731)) and (la.exact("English"))	129535
S52	((s44 or s45 or s46 or s47 or s48 or s49 or s50 or s51)) and (pd(>20130731)) and (la.exact("English"))	982492
S53	((S37 OR S43 OR S52)) and (pd(>20130731)) and (la.exact("English"))	1369894
S54	((S25 AND (S37 OR S43 OR S52))) and (pd(>20130731)) and (la.exact("English"))	2191
S55	((S29 AND (S37 OR S43 OR S52))) and (pd(>20130731)) and (la.exact("English"))	n=2031

Search results

Medline = 2031; Embase = 4125; Cochrane Library = 291

Total: all databases – without duplicates/triplicates: n=5142

B Transmitted drug resistance

No PICO

Questions:

What are the optimal regimens in the context of transmitted drug resistance?
 What are the implications of transmitted drug resistance on resistance to other classes (e.g. evidence to support integrase inhibitor resistance testing when there is major nucleoside reverse transcriptase inhibitor (NRTI), NNRTI or PI transmitted drug resistance)?

Search: Medline, Embase and Cochrane Library: August 2014 to March 2021

Medline and Embase limited also to English only, adults, humans and type of study (randomised controlled trials, systematic reviews and observational studies)

ProQuest® Medline

Set#	Searched for	Results
S1	(MESH.EXACT("AIDS Serodiagnosis") OR MESH.EXACT.EXPLODE("HIV Infections") OR MESH.EXACT.EXPLODE("HIV") OR MESH.EXACT("HIV Long-Term Survivors"))	312844
S2	(ti,ab(HIV or HIV1 or HIV2 or "human immun* deficien[*3]" or PLWH or AIDS near/3 virus or "acquired immun* deficien[*3]"))	310005
S3	(ti,ab("human immunodeficiency virus" or "human immunodeficiency virus" or "human immunodeficiency virus" or "human immune-deficiency virus"))	85464
S4	(ti,ab("acquired immunodeficiency syndrome" or "acquired immunodeficiency syndrome" or "acquired immuno-deficiency syndrome" or "acquired immune-deficiency syndrome"))	21526

S5	(s1 or s2 or s3 or s4)	398782
S6	(ti,ab(transmitted near/3 resistance))	880
S7	(MESH.EXACT.EXPLODE("Anti-Retroviral Agents"))	81702
S8	(ti,ab(antiretroviral or anti-retroviral))	61608
S9	(S7 OR S8)	111397
S10	(S5 AND S6)	695
S11	(S10 AND S9)	571
S12	(s11) and (la.exact("English"))	564
S13	(s11) and (pd(>20131231)) and (la.exact("English"))	262
S14	((S13 and human(yes))) and (pd(>20131231)) and (la.exact("English"))	221
S15	((S13 not (human(yes) or animal(yes)))) and (pd(>20131231)) and (la.exact("English"))	41
S16	((S14 OR S15)) and (pd(>20131231)) and (la.exact("English"))	262
S17	((MESH.EXACT.EXPLODE("Child") OR MESH.EXACT.EXPLODE("Infant") OR ti,ab(child* or neonat* or infant*)) and (pd(>20131231)) and (la.exact("English"))	590885
S18	((MESH.EXACT.EXPLODE("Adult") OR ti,ab(adult*)) and (pd(>20131231)) and (la.exact("English"))	1711671
S19	((S17 NOT S18)) and (pd(>20131231)) and (la.exact("English"))	384080
S20	((S16 NOT S19)) and (pd(>20131231)) and (la.exact("English"))	250
S21	((MESH.EXACT("Randomized Controlled Trials as Topic") or MESH.EXACT("Random Allocation") or MESH.EXACT("Double Blind Method") or MESH.EXACT("Single Blind Method")) and (pd(>20131231)) and (la.exact("English"))	98198
S22	((Rtype.exact("clinical trial, phase i")) and (pd(>20131231)) and (la.exact("English"))	6233
S23	((Rtype.exact("clinical trial, phase ii")) and (pd(>20131231)) and (la.exact("English"))	9936
S24	((Rtype.exact("clinical trial, phase iii")) and (pd(>20131231)) and (la.exact("English"))	7589
S25	((Rtype.exact("clinical trial, phase iv")) and (pd(>20131231)) and (la.exact("English"))	917
S26	((Rtype.exact("controlled clinical trial")) and (pd(>20131231)) and (la.exact("English"))	5286
S27	((Rtype.exact("randomized controlled trial")) and (pd(>20131231)) and (la.exact("English"))	127586
S28	((Rtype.exact("multicenter study")) and (pd(>20131231)) and (la.exact("English"))	97332

S29	((Rtype.exact("clinical trial"))) and (pd(>20131231)) and (la.exact("English"))	36274
S30	((MESH.EXACT.EXPLODE("clinical trials as topic") or MESH.EXACT("placebos"))) and (pd(>20131231)) and (la.exact("English"))	67098
S31	((ti,ab(clinical near/1 trial*))) and (pd(>20131231)) and (la.exact("English"))	146162
S32	((ti,ab((singl* or doubl* or treb* or tripl*) near/1 (blind* or mask*)))) and (pd(>20131231)) and (la.exact("English"))	43761
S33	((ti,ab(placebo* or "randomly allocated" or (allocated near/2 random*)))) and (pd(>20131231)) and (la.exact("English"))	67650
S34	((s21 or s22 or s23 or s24 or s25 or s26 or s27 or s28 or s29 or s30 or s31 or s32 or s33)) and (pd(>20131231)) and (la.exact("English"))	444371
S35	((MESH.EXACT("Meta-Analysis as Topic"))) and (pd(>20131231)) and (la.exact("English"))	3988
S36	((ti,ab("meta analy*" or metaanaly*))) and (pd(>20131231)) and (la.exact("English"))	105677
S37	(Rtype.EXACT("Meta-Analysis")) and (pd(>20131231)) and (la.exact("English"))	63385
S38	((ti,ab(systematic near/1 (review* or overview*)))) and (pd(>20131231)) and (la.exact("English"))	114861
S39	((MESH.EXACT.EXPLODE("Review Literature as Topic") or MESH.EXACT("Meta-Analysis as Topic"))) and (pd(>20131231)) and (la.exact("English"))	8649
S40	((s35 or s36 or s37 or s38 or s39)) and (pd(>20131231)) and (la.exact("English"))	174187
S41	((MESH.EXACT.EXPLODE("case control studies") or MESH.EXACT("Epidemiologic studies") or MESH.EXACT.EXPLODE("cohort studies"))) and (pd(>20131231)) and (la.exact("English"))	669781
S42	((ti,ab("case control"))) and (pd(>20131231)) and (la.exact("English"))	47460
S43	((ti,ab(cohort near/1 (study or studies)))) and (pd(>20131231)) and (la.exact("English"))	122893
S44	((ti,ab("Cohort analy*"))) and (pd(>20131231)) and (la.exact("English"))	4184
S45	((ti,ab("follow up" near/1 (study or studies)))) and (pd(>20131231)) and (la.exact("English"))	15070
S46	((ti,ab(observational near/1 (study or studies)))) and (pd(>20131231)) and (la.exact("English"))	69264
S47	((ti,ab(Longitudinal or Retrospective or "Cross sectional"))) and (pd(>20131231)) and (la.exact("English"))	485162
S48	((MESH.EXACT("Cross-sectional studies"))) and (pd(>20131231)) and (la.exact("English"))	138199
S49	((s41 or s42 or s43 or s44 or s45 or s46 or s47 or s48)) and (pd(>20131231)) and (la.exact("English"))	1049528
S50	((s34 or s40 or s49)) and (pd(>20131231)) and (la.exact("English"))	1463969

S51	((S16 AND (S34 OR S40 OR S49))) and (pd(>20131231)) and (la.exact("English"))	n=103
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Search results

Medline = 103; Embase = 172; Cochrane Library = 12

Total of all databases without duplicates/triplicates: n=231

3 Supporting patients

Switching therapy (simplification)

No PICO

Questions:

1. What are the benefits and disadvantages (and what is the overall balance) of simplifying from conventional ART to PI-based or dual therapy?
2. What are the benefits and disadvantages (and what is the overall balance) of simplifying from conventional ART to integrase inhibitor monotherapy?
3. In patients suppressed on conventional ART (two NRTIs + efavirenz 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, NNRTI → integrase inhibitor or alternative NNRTI, alternative NNRTI or integrase inhibitor)?

Search: Medline, Embase and Cochrane Library: January 2014 to March 2021

Medline and Embase limited also to English only, adults, humans and type of study (randomised controlled trials, systematic reviews and observational studies)

ProQuest® Medline

Set#	Searched for	Results
S1	(MESH.EXACT("AIDS Serodiagnosis") OR MESH.EXACT.EXPLODE("HIV Infections") OR MESH.EXACT.EXPLODE("HIV") OR MESH.EXACT("HIV Long-Term Survivors"))	312301
S2	(ti,ab(HIV or HIV1 or HIV2 or "human immun* deficien[*3]" or PLWH or AIDS near/3 virus or "acquired immun* deficien[*3]"))	309401
S3	(ti,ab("human immunodeficiency virus" or "human immunodeficiency virus" or "human immunodeficiency virus" or "human immune-deficiency virus"))	85321
S4	(ti,ab("acquired immunodeficiency syndrome" or "acquired immunodeficiency syndrome" or "acquired immuno-deficiency syndrome" or "acquired immune-deficiency syndrome"))	21511
S5	(s1 or s2 or s3 or s4)	398104
S6	(MESH.EXACT.EXPLODE("Anti-Retroviral Agents"))	81514
S7	(MESH.EXACT("Antiretroviral Therapy, Highly Active"))	20889
S8	ti,ab(HAART)	11773
S9	(ti,ab((antiretroviral or anti-retroviral) near/3 (therap* or treat* or agent* or drug* or medication* or regime*)))	57499
S10	(ti,ab(NRTI* or NNRTI*))	4961

S11	(ti,ab((nucleoside or non-nucleoside or nonnucleoside) near/2 "reverse transcriptase inhibitor*"))	6528
S12	(ti,ab((protease or integrase) near/1 inhibitor*))	34349
S13	(ti,ab((anti-HIV or anti-aids) near/1 (drug* or agent* or therap* or treat* or agent* or regime*)))	4065
S14	(s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13)	137861
S15	(ti,ab(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))	34812
S16	(ti,ab(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 tivicy or vitekta or isentress))	1996
S17	(ti,ab(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))	1000
S18	(ti,ab(Biktarvy or bictegravir or tenofovir alafenamide or doravirine or Pifeltro or Delstrigo or Descovy or cabotegravir))	555
S19	(s15 or s16 or s17 or s18)	35775
S20	(S14 OR S19)	142995
S21	(ti,ab((switch* or stop* or change* or changing or discontinue* or interrupt* or withdraw* or substitute* or cessation or ceas*) near/3 ("third agent" or backbone or treatment or regim* or therap* or drug* or anti-retroviral* or antiretroviral* or HAART or ART)))	176395
S22	(ti,ab((switch* or stop* or change* or changing or discontinue* or interrupt* or withdraw* or substitute* or cessation or ceas*) near/3 (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 tivicy 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)))	1976
S23	(ti,ab(maintenance near/3 (mono-therap* or monotherapy* or therap* or regim*)))	18484
S24	(ti,ab (switch* or simplify*))	39
S25	(ti,ab((stop* or ceas* or cessation or discontinue* or withdraw*) near/3 (staggered or simultaneous)))	231
S26	(MESH.EXACT("Withholding Treatment"))	11565

S27	(s21 or s22 or s23 or s24 or s25 or s26)	20414
S28	(S5 AND S20)	104895
S29	(S28 AND S27)	8433
S30	(s29) and (la.exact("English"))	8047
S31	(s29) and (pd(>20131231)) and (la.exact("English"))	2680
S32	((S31 and human(yes))) and (pd(>20131231)) and (la.exact("English"))	1952
S33	((S31 not (human(yes) or animal(yes)))) and (pd(>20131231)) and (la.exact("English"))	688
S34	((S32 OR S33)) and (pd(>20131231)) and (la.exact("English"))	2639
S35	((MESH.EXACT.EXPLODE("Child") OR MESH.EXACT.EXPLODE("Infant") OR ti,ab(child* or neonat* or infant*)) and (pd(>20131231)) and (la.exact("English"))	586027
S36	((MESH.EXACT.EXPLODE("Adult") OR ti,ab(adult*)) and (pd(>20131231)) and (la.exact("English"))	1697144
S37	((S35 NOT S36)) and (pd(>20131231)) and (la.exact("English"))	380984
S38	((S34 NOT S37)) and (pd(>20131231)) and (la.exact("English"))	2463
S39	((MESH.EXACT("Randomized Controlled Trials as Topic") or MESH.EXACT("Random Allocation") or MESH.EXACT("Double Blind Method") or MESH.EXACT("Single Blind Method"))) and (pd(>20131231)) and (la.exact("English"))	97422
S40	((Rtype.exact("clinical trial, phase i")) and (pd(>20131231)) and (la.exact("English"))	6184
S41	((Rtype.exact("clinical trial, phase ii")) and (pd(>20131231)) and (la.exact("English"))	9832
S42	((Rtype.exact("clinical trial, phase iii")) and (pd(>20131231)) and (la.exact("English"))	753
S43	((Rtype.exact("clinical trial, phase iv")) and (pd(>20131231)) and (la.exact("English"))	904
S44	((Rtype.exact("controlled clinical trial")) and (pd(>20131231)) and (la.exact("English"))	5262
S45	((Rtype.exact("randomized controlled trial")) and (pd(>20131231)) and (la.exact("English"))	126596
S46	((Rtype.exact("multicenter study")) and (pd(>20131231)) and (la.exact("English"))	96376
S47	((Rtype.exact("clinical trial")) and (pd(>20131231)) and (la.exact("English"))	36014
S48	((MESH.EXACT.EXPLODE("clinical trials as topic")) and (pd(>20131231)) and (la.exact("English"))	64258
S49	((ti,ab(clinical near/1 trial*)) and (pd(>20131231)) and (la.exact("English"))	144881

S50	((ti,ab((singl* or doubl* or treb* or tripl*) near/1 (blind* or mask*)))) and (pd(>20131231)) and (la.exact("English"))	43401
S51	(MESH.EXACT("placebos")) and (pd(>20131231)) and (la.exact("English"))	2598
S52	((ti,ab(placebo* or "randomly allocated" or allocated near/2 random*))) and (pd(>20131231)) and (la.exact("English"))	67076
S53	((s39 or s40 or s41 or s42 or s43 or s44 or s45 or s46 or s47 or s48 or s49 or s50 or s51 or s52)) and (pd(>20131231)) and (la.exact("English"))	440653
S54	((MESH.EXACT("Meta-Analysis as Topic"))) and (pd(>20131231)) and (la.exact("English"))	3953
S55	((ti,ab("meta analy*" or metaanaly*))) and (pd(>20131231)) and (la.exact("English"))	104625
S56	(Rtype.EXACT("Meta-Analysis")) and (pd(>20131231)) and (la.exact("English"))	62759
S57	((ti,ab(systematic near/1 (review* or overview*)))) and (pd(>20131231)) and (la.exact("English"))	113639
S58	((MESH.EXACT.EXPLODE("Review Literature as Topic") or MESH.EXACT("Meta-Analysis as Topic"))) and (pd(>20131231)) and (la.exact("English"))	8577
S59	((s54 or s55 or s56 or s57 or s58)) and (pd(>20131231)) and (la.exact("English"))	172531
S60	((MESH.EXACT("Epidemiologic studies") or MESH.EXACT.EXPLODE("case control studies") or MESH.EXACT.EXPLODE("cohort studies") or MESH.EXACT("Cross-sectional studies"))) and (pd(>20131231)) and (la.exact("English"))	768048
S61	((ti,ab("case control")))) and (pd(>20131231)) and (la.exact("English"))	47073
S62	((ti,ab(cohort near/1 (study or studies)))) and (pd(>20131231)) and (la.exact("English"))	121631
S63	((ti,ab("Cohort analy*")))) and (pd(>20131231)) and (la.exact("English"))	4141
S64	((ti,ab("follow up" near/1 (study or studies)))) and (pd(>20131231)) and (la.exact("English"))	14948
S65	((ti,ab(observational near/1 (study or studies)))) and (pd(>20131231)) and (la.exact("English"))	68597
S66	((ti,ab(Longitudinal or Retrospective or "Cross sectional")))) and (pd(>20131231)) and (la.exact("English"))	480475
S67	((s60 or s61 or s62 or s63 or s64 or s65 or s66)) and (pd(>20131231)) and (la.exact("English"))	1040059
S68	((S53 OR S59 OR S67)) and (pd(>20131231)) and (la.exact("English"))	1451060
S69	((S34 AND (S53 OR S59 OR S67))) and (pd(>20131231)) and (la.exact("English"))	1541
S70	(S38 AND (S53 OR S59 OR S67))	n=1435

Search results

Medline = 1435; Embase = 3223; Cochrane Library = 1180

Total all databases (without duplicates/triplicates): n=4619

4 When to start

A Immediate ART after diagnosis

Population: People with recently diagnosed HIV infection (excluding those with cryptococcal or tuberculous meningitis)

Intervention: Starting ART immediately at diagnosis (on day of diagnosis or within days)

Comparator: Starting ART once all baseline investigations have been completed

Outcomes: Death, retention in care/loss to follow-up, proportion of population established on ART, drug adverse events, development of drug resistance, HIV transmission, switching of regimen, patient satisfaction

Question: In a person with newly diagnosed HIV infection (excluding those with cryptococcal or tuberculous meningitis, where immediate therapy is clearly associated with increased harm), is there benefit in starting treatment immediately?

B. Starting ART in elite controllers

Population: People with viral load below the limit of detection (<200 copies/mL) and CD4 count >500 cells/mm³ without treatment

Intervention: Starting ART

Comparator: Deferring ART

Outcomes: Death, incidence of AIDS and no-AIDS events, retention in care/loss to follow-up, drug adverse events, development of drug resistance, HIV transmission, patient satisfaction

Question. In elite controllers, is there benefit in starting ART immediately (with any combination)?

Search (A and B): Medline, Embase and Cochrane Library: January 2014 to March 2021

Medline and Embase limited also to English only, adults, humans and type of study (randomised controlled trials, systematic reviews and observational studies)

ProQuest® Medline

Set#	Searched for	Results
S1	(MESH.EXACT.EXPLODE("HIV Infections") OR MESH.EXACT.EXPLODE("HIV") OR MESH.EXACT("HIV Long-Term Survivors"))	311409
S2	(ti,ab(HIV or HIV1 or HIV2 or "human immun* deficien[*3]" or PLWH))	305065
S3	(ti,ab("human immunodeficiency virus" or "human immunodeficiency virus" or "human immunodeficiency virus" or "human immune-deficiency virus"))	85373

S4	(s1 or s2 or s3)	395242
S5	(MESH.EXACT("AIDS Serodiagnosis"))	6631
S6	(ti,ab(AIDS near/3 virus or "acquired immun* deficien[*3]"))	8568
S7	(ti,ab("acquired immunodeficiency syndrome" or "acquired immunodeficiency syndrome" or "acquired immuno-deficiency syndrome" or "acquired immune-deficiency syndrome"))	21516
S8	(s5 or s6 or s7)	30123
S9	(S4 OR S8)	398389
S10	(ti,ab("elite control*" or "HIV control*" or "viremic control*" or "viraemic control*"))	1465
S11	(ti,ab(undetected near/3 virus or viral or "viral load"))	338527
S12	(S10 OR S11)	339396
S13	(ti,ab((early or earlier or immediate* or delay* or defer* or later or when or wait) near/3 (begin* or start* or initiate* or commence*)))	79730
S14	(ti,ab((early or earlier or immediate* or delay* or defer* or later or when or wait) near/3 (therap* or anti-retroviral* or antiretroviral* or HAART or ART)))	79527
S15	(S13 OR S14)	151687
S16	(S9 AND S15)	7839
S17	(S4 AND S12)	60372
S18	(S17 AND S15)	2139
S19	(s16) and (la.exact("English"))	7358
S20	(s16) and (pd(>20131231)) and (la.exact("English"))	2773
S21	((S20 and human(yes))) and (pd(>20131231)) and (la.exact("English"))	2063
S22	((S20 not (human(yes) or animal(yes)))) and (pd(>20131231)) and (la.exact("English"))	688
S23	((S21 OR S22)) and (pd(>20131231)) and (la.exact("English"))	2750
S24	((MESH.EXACT.EXPLODE("Child") OR MESH.EXACT.EXPLODE("Infant") OR ti,ab(child* or neonat* or infant*)) and (pd(>20131231)) and (la.exact("English"))	588248
S25	((MESH.EXACT.EXPLODE("Adult") OR ti,ab(adult*)) and (pd(>20131231)) and (la.exact("English"))	1704417
S26	((S24 NOT S25)) and (pd(>20131231)) and (la.exact("English"))	382365

S27	((S23 NOT S26)) and (pd(>20131231)) and (la.exact("English"))	2401
S28	(s18) and (la.exact("English"))	2051
S29	(s18) and (pd(>20131231)) and (la.exact("English"))	808
S30	((S29 and human(yes))) and (pd(>20131231)) and (la.exact("English"))	563
S31	((S29 not (human(yes) or animal(yes)))) and (pd(>20131231)) and (la.exact("English"))	235
S32	((S30 OR S31)) and (pd(>20131231)) and (la.exact("English"))	798
S33	((MESH.EXACT.EXPLODE("Child") OR MESH.EXACT.EXPLODE("Infant") OR ti,ab(child* or neonat* or infant*))) and (pd(>20131231)) and (la.exact("English"))	588248
S34	((MESH.EXACT.EXPLODE("Adult") OR ti,ab(adult*))) and (pd(>20131231)) and (la.exact("English"))	1704417
S35	((S33 NOT S34)) and (pd(>20131231)) and (la.exact("English"))	382365
S36	((S32 NOT S35)) and (pd(>20131231)) and (la.exact("English"))	691
S37	((MESH.EXACT("Randomized Controlled Trials as Topic") or MESH.EXACT("Random Allocation") or MESH.EXACT("Double Blind Method") or MESH.EXACT("Single Blind Method"))) and (pd(>20131231)) and (la.exact("English"))	97832
S38	((Rtype.exact("clinical trial, phase i") or Rtype.exact("clinical trial, phase ii") or Rtype.exact("clinical trial, phase iii") or Rtype.exact("clinical trial, phase iv") or Rtype.exact("controlled clinical trial") or Rtype.exact("randomized controlled trial") or Rtype.exact("multicenter study") or Rtype.exact("clinical trial"))) and (pd(>20131231)) and (la.exact("English"))	237866
S39	((MESH.EXACT.EXPLODE("clinical trials as topic"))) and (pd(>20131231)) and (la.exact("English"))	64596
S40	((ti,ab(clinical near/1 trial*))) and (pd(>20131231)) and (la.exact("English"))	145422
S41	((ti,ab((singl* or doubl* or treb* or tripl*) near/1 (blind* or mask*))) and (pd(>20131231)) and (la.exact("English"))	43561
S42	(MESH.EXACT("placebos")) and (pd(>20131231)) and (la.exact("English"))	2608
S43	((ti,ab(placebo* or "randomly allocated" or allocated near/2 random*))) and (pd(>20131231)) and (la.exact("English"))	67306
S44	((s37 or s38 or s39 or s40 or s41 or s42 or s43)) and (pd(>20131231)) and (la.exact("English"))	442412
S45	((MESH.EXACT("Meta-Analysis as Topic"))) and (pd(>20131231)) and (la.exact("English"))	3974
S46	((ti,ab("meta analy*" or metaanaly*))) and (pd(>20131231)) and (la.exact("English"))	105043
S47	(Rtype.EXACT("Meta-Analysis")) and (pd(>20131231)) and (la.exact("English"))	63094

S48	((ti,ab(systematic near/1 (review* or overview*)))) and (pd(>20131231)) and (la.exact("English"))	114107
S49	((MESH.EXACT.EXPLODE("Review Literature as Topic") or MESH.EXACT("Meta-Analysis as Topic")) and (pd(>20131231)) and (la.exact("English"))	8612
S50	(s45 or s46 or s47 or s48 or s49)	173171
S51	((MESH.EXACT("Epidemiologic studies") or MESH.EXACT.EXPLODE("case control studies") or MESH.EXACT.EXPLODE("cohort studies") or MESH.EXACT("Cross-sectional studies")) and (pd(>20131231)) and (la.exact("English"))	771740
S52	((ti,ab("case control")) and (pd(>20131231)) and (la.exact("English"))	47226
S53	((ti,ab(cohort near/1 (study or studies)))) and (pd(>20131231)) and (la.exact("English"))	122172
S54	((ti,ab("Cohort analy*")) and (pd(>20131231)) and (la.exact("English"))	4163
S55	((ti,ab("follow up" near/1 (study or studies)))) and (pd(>20131231)) and (la.exact("English"))	15002
S56	((ti,ab(observational near/1 (study or studies)))) and (pd(>20131231)) and (la.exact("English"))	68890
S57	((ti,ab(Longitudinal or Retrospective or "Cross sectional")) and (pd(>20131231)) and (la.exact("English"))	482513
S58	((s51 or s52 or s53 or s54 or s55 or s56 or s57)) and (pd(>20131231)) and (la.exact("English"))	1044501
S59	((S44 OR S50 OR S58)) and (pd(>20131231)) and (la.exact("English"))	1456990
S60	((S27 AND (S44 OR S50 OR S58))) and (pd(>20131231)) and (la.exact("English"))	A: n=1291
S61	((S23 AND (S44 OR S50 OR S58))) and (pd(>20131231)) and (la.exact("English"))	1505
S62	((s61 not s60)) and (pd(>20131231)) and (la.exact("English"))	214
S63	((S36 AND (S44 OR S50 OR S58))) and (pd(>20131231)) and (la.exact("English"))	B: n=362

Search results

A Immediate ART

Medline = 1291; Embase = 1952; Cochrane Library = 545

Total of all databases – without duplicates/triplicates: n=2774

B Elite controllers

Medline = 362; Embase = 593; Cochrane Library = 211

Total of all databases – without duplicates/triplicates: n=876