Title: What ARV regimen to start with in adults, adolescents and pregnant women living with HIV-2?

Contents

1. PICO question

	What ARV regimen to start (HIV-2)
P	Adults, pregnant women, adolescents living with HIV-2 or HIV-1 and HIV-2
I	ART initiation with a PI-based regimens
C	ART initiation with a triple NRTI regimen
O	Mortality, morbidity, vertical transmission, severe adverse events, viral response, CD4 response adherence, retention, switching rate, tolerability, TB incidence

2. Search strategy

We developed a sensitive search strategy that combined terms for HIV-2 and ART (HAART or antiretroviral therapy or highly active or antiretroviral or therapy or highly active antiretroviral therapy, drug resistance, viral drug resistance).

("hiv-2"[MeSH Terms] OR "hiv-2"[All Fields] OR "hiv 2"[All Fields]) AND ("drug resistance, viral"[MeSH Terms] OR ("drug"[All Fields] AND "resistance"[All Fields] AND "viral"[All Fields]) OR "viral drug resistance"[All Fields] OR ("drug"[All Fields] AND "resistance"[All Fields] AND "viral"[All Fields]) OR "drug resistance, viral"[All Fields]) AND ("1996"[PDAT] : "2012"[PDAT]):

("hiv-2"[MeSH Terms] OR "hiv-2"[All Fields] OR "hiv 2"[All Fields]) AND ("antiretroviral therapy, highly active"[MeSH Terms] OR ("antiretroviral"[All Fields] AND "therapy"[All Fields] AND "highly"[All Fields] AND "active"[All Fields]) OR "highly active antiretroviral therapy"[All Fields] OR "haart"[All Fields]) AND ("1996"[PDAT]: "2012"[PDAT])

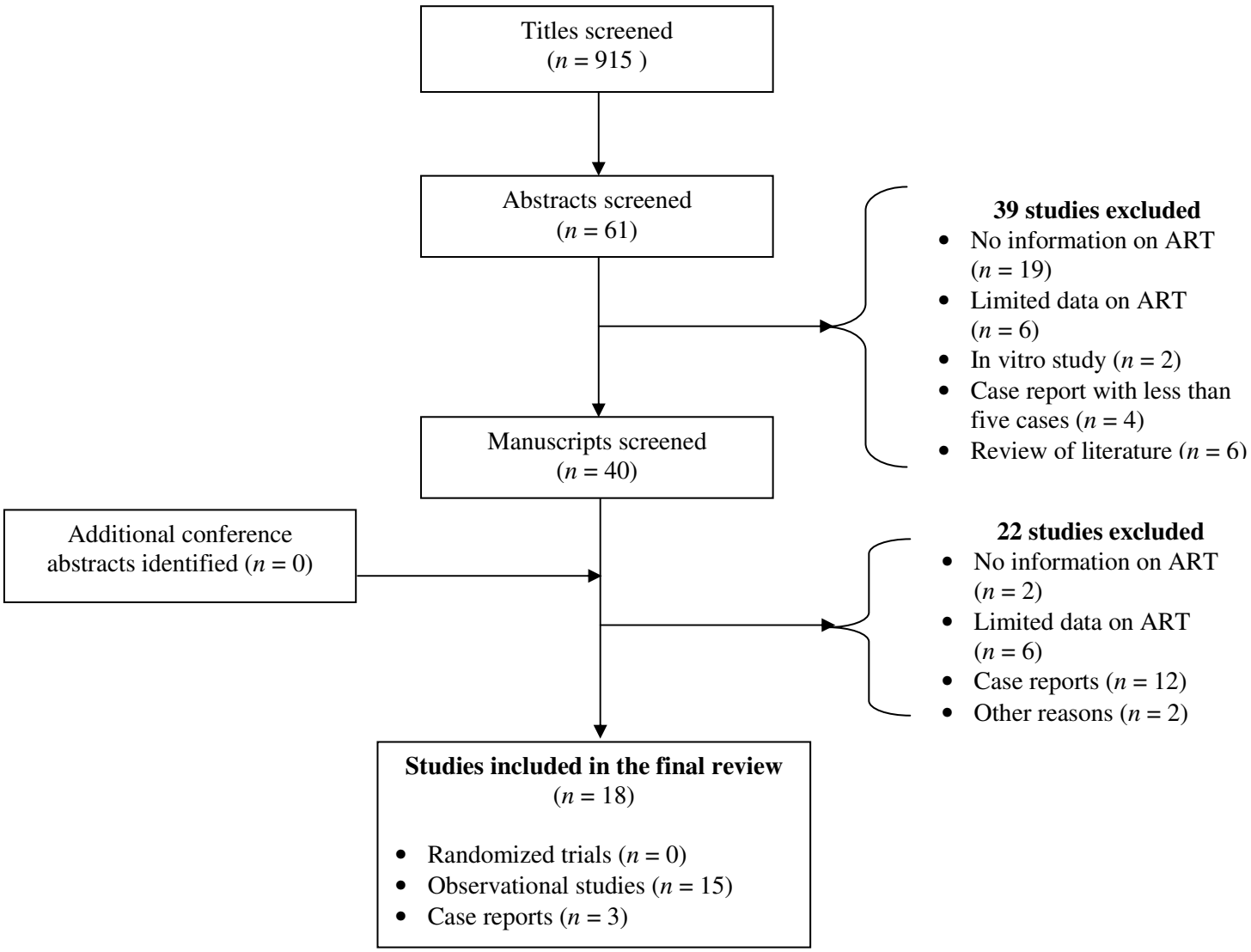
Initial searches were developed for the following databases (from 1996 to 1 November 2012): MEDLINE via PubMed, EMBASE, LILACS, Web of Science, Current Controlled Trials (www.controlled-trials.com) and the Cochrane Central Register of Controlled Trials. The MEDLINE search was subsequently updated to 1 November 2012. We also searched the data available on the web sites of the International AIDS Society (IAS) conferences and of the Conference on Retroviruses and Opportunistic Infections (CROI). We particularly searched for abstracts from conferences held between July 2009 and July 2012 to identify studies that were recently completed but may not yet be published as full-text articles. Bibliographies of

relevant review articles and other papers were also screened. One of the authors did a preliminary search, scanning all titles for eligibility according to the predefined inclusion criteria. The full abstracts of potentially eligible studies were then scanned by additional two reviewers, who worked independently to select potentially relevant full-text articles. Once all relevant full-text articles were reviewed, final agreement on including studies was determined through consensus.

Comments

A total of 18 reports were included in the final review according to our eligibility criteria. There were no randomized trials, 15 cohort studies and 3 case series. No study (RCT or observational study) has addressed when to start ART in HIV-2 infection identified in our review.

3. Flow diagram of screening process



4. Evidence summaries

4.1. Observational studies on HIV-2

Initiation of antiretroviral therapy (ART) among people living with HIV-2

Outcome: mortality

This outcome was reported in seven cohorts without breaking down this outcome by drug regimen (PI-based regimen versus three NRTIs) (Table 7). Bernard et al. reported 2/29 deaths (7%) among people living with HIV-2 treated with lopinavir/ritonavir in France (1). According to the European Cohort data, no death was reported during the first 12 months of follow-up among 170 people living with HIV-2 (126 initiated a PI-based regimen and 44 initiated a three-NRTI-based regimen) (2). Two data from low- and middle-income countries reported mortality, one from Gambia with 6 deaths reported among 51 (12%) people living with HIV-2. In this latter study, the survival rate was 96% at 12 months (3). Finally, Harries et al. reported in Burkina-Faso 14 deaths among 91 people living with HIV-2 (15%) (4). The crude mortality among people living with HIV-2 was estimated at 4% (30/697).

The quality of evidence is very low and was downgraded for imprecision (few events) and risk of bias. Only unadjusted data were available to address this question. The time of observation by drug regimen was not reported.

Outcome: increase in CD4 cell count 24 and 48 weeks after ART initiation

Four studies reported the immune response at 24 weeks: one from Côte d'Ivoire (n = 18) (5), one from the Netherlands (n = 13) (6), one in France (n = 61) (7) and last one in India (8) (Table 4). All patients in the four studies initiated a PI-based regimen, mainly with nelfinavir in Côte d'Ivoire (5) and indinavir in the Netherlands (6) and in India (8). Of note, in France, 77% were on a PI-based regimen versus 23% initiating three NRTIs. The mean CD4 cell count increase at 24 weeks after ART initiation was 84 cells/mm^3 (range: +41 to +150) cells/mm^3. In the study in France (7), the median CD4 cell count did not differ between patients treated with a PI-containing regimen and those without, at month 6 (P = 0.47) and month 24 (P = 0.68) after treatment initiation. At week 24, in the group of patients without PI (n = 10), the CD4 cell increase was +57 (+37 to +100) cells/mm^3, whereas it was +52 (+8 to +81) cells/mm^3 among 40 people living with HIV-2 initiating a PI-containing regimen (7).

The immune response at 48 weeks was reported in six studies (Table 4), one from Côte d'Ivoire (n = 18) (5), one from western Africa with the enrolment of 270 patients (9), one in India (8) and three from high-income countries: the Netherlands (n = 13) (6) France (n = 61 patients) (7) and one from the European cohort (n = 170) (2). Overall, the mean CD4 cell count increase at 48 weeks after ART initiation was 101 (range: +45 to +180) cells/mm^3. In France at 48 weeks in the group of patients without PI (n = 9), the CD4 cell increase was +71 (+0 to +90) cells/mm^3, whereas it was +58 (+11 to +130) cells/mm^3 among 29 people living with HIV-2 initiating a PI-containing regimen (7). The reported data of four of the studies are inadequate to test the significance of these differences by drug regimens (PI-based regimen versus three NRTIs). Only one study presents the immune response at week 48 by drug regimen initiated (2). Beyond 3 months of treatment, the estimated CD4 cell count decreased among patients treated with three NRTIs and increased among those treated with PI/r (–60 versus +176 cells/mm^3/year; P = 0.002). These

changes resulted in estimated CD4 cell counts at month 12 being lower among patients treated with three NRTIs than among patients treated with PI/r (191 versus 327 cells/mm^3; $P = 0.001$). The difference in estimated CD4 cell counts at month 12 between patients treated with three NRTIs and those treated with PI/r remained statistically significant after adjustment for geographical origin ($P = 0.0009$) or for baseline HIV-2 RNA level ($P = 0.05$).

The quality of the evidence is very low and is downgraded for imprecision (few events) and risk of bias (no adjustment for confounders).

Outcome: viral response

The threshold of detection of viral load is variable (100, 400 or 500 copies). In addition, we found that between 10% and 39% of the people living with HIV-2 who initiated antiretroviral therapy had undetectable viral load. In Gambia (3), 81% of the patients enrolled had a viral load of <400 copies. Ruelle et al. (10) in Belgium and Luxembourg reported that 3 of 13 (62%) people with HIV-2 initiating a PI-based regimen had undetectable viral load versus 1 of 6 (17%) among those initiating a regimen without PI (10). Three studies presented the viral response among patients initiating a PI-based regimen or without a PI-based regimen. Matheron et al. (7) reported a median change (interquartile range) of viral load ($\log_{10}$ copies/ml) of –1.0 (–1.0 to 0) among patients without PI and –0.6 (–1.7 to 0) $\log_{10}$ copies/ml among patients initiating PI. A similar report in the same group using European cohort data reported a change of –1.8 $\log_{10}$ copies/ml among patients initiating a PI-based regimen and 0 log among patients initiating three NRTIs (2). Table 5 describes the viral response among people living with HIV-2 receiving ART.

The quality of the evidence is very low and is downgraded for imprecision (few events) and risk of bias (no adjustment for confounders). The results of this study were limited because of sample size limited.

Outcome: adverse events

No studies reported adverse events or the data reported were limited.

Outcome: drug resistance

Seven of 18 studies reported information on the viral resistance mutations of different ARV medicines used. However, the quality of the data are limited and the outcomes are variable.

The quality of the evidence is very low and is downgraded for imprecision (few events) and risk of bias (no adjustment for confounders). The results of this study were limited because of limited sample size.

Outcome: clinical progression to AIDS

Three of 18 studies reported information on clinical progression to AIDS among people receiving ART. However, the details of the data reported are limited. In the French cohort, among 29 people living with HIV-2 treated with PI-based therapy enrolled, none of the 18 patients with CDC stage A at baseline progressed during follow-up. Two patients died, one from bladder cancer and one from lung cancer (1). In the European cohort, among the 170 people living with HIV-2 enrolled (44 on three NRTIs), one patient (2%) receiving a triple NRTI regimen experienced progression to AIDS (tuberculosis) 5 months after treatment initiation. Patients who progressed to AIDS were 9 (7%) in those treated with PI/r

(cytomegalovirus infections [2], recurrent bacterial pneumonia [1], candidiasis [1], toxoplasmosis [1], cryptococcosis [1], pneumocystosis [1], HIV wasting syndrome [1] and unknown [1]) within a median delay of 2 months (range 0.5–7.5) after treatment initiation (2). Matheron et al. (7) reported in France that 3 of 61 (5%) patients initiating LPV/r progressed to AIDS, and in the Netherlands study, 15% of patients had presented clinical progression to AIDS (6).

The quality of the evidence is very low and is downgraded for imprecision (few events) and risk of bias (no adjustment for confounders). The results of this study were limited because of sample size limited.

References

1. Benard A, Damond F, Campa P, Peytavin G, Descamps D, Lascoux-Combes C, et al. Good response to lopinavir/ritonavir-containing antiretroviral regimens in antiretroviral-naive HIV-2-infected patients. AIDS 2009;23(9):1171-3.

2. Benard A, van Sighem A, Taieb A, Valadas E, Ruelle J, Soriano V, et al. Immunovirological response to triple nucleotide reverse-transcriptase inhibitors and ritonavir-boosted protease inhibitors in treatment-naive HIV-2-infected patients: the ACHI(E)V(2E) Collaboration Study Group. Clinical Infectious Diseases 2011;52(10):1257-66.

3. Peterson I, Togun O, de Silva T, Oko F, Rowland-Jones S, Jaye A, et al. Mortality and immunovirological outcomes on antiretroviral therapy in HIV-1 and HIV-2-infected individuals in the Gambia. AIDS 2011;25(17):2167-75.

4. Harries K, Zachariah R, Manzi M, Firmenich P, Mathela R, Drabo J, et al. Baseline characteristics, response to and outcome of antiretroviral therapy among patients with HIV-1, HIV-2 and dual infection in Burkina Faso. Transactions of the Royal Society of Tropical Medicine and Hygiene 2010;104(2):154-61.

5. Adje-Toure CA, Cheingsong R, Garcia-Lerma JG, Eholie S, Borget MY, Bouchez JM, et al. Antiretroviral therapy in HIV-2-infected patients: changes in plasma viral load, $CD4^+$ cell counts, and drug resistance profiles of patients treated in Abidjan, Côte d'Ivoire. AIDS 2003;17(Suppl 3):S49-S54.

6. van der Ende ME, Prins JM, Brinkman K, Keuter M, Veenstra J, Danner SA, et al. Clinical, immunological and virological response to different antiretroviral regimens in a cohort of HIV-2-infected patients. AIDS 2003;17(Suppl 3):S55-S61.

7. Matheron S, Damond F, Benard A, Taieb A, Campa P, Peytavin G, et al. CD4 cell recovery in treated HIV-2-infected adults is lower than expected: results from the French ANRS CO5 HIV-2 cohort. AIDS 2006 14;20(3):459-62.

8. Chiara M, Rony Z, Homa M, Bhanumati V, Ladomirska J, Manzi M, et al. Characteristics, immunological response & treatment outcomes of HIV-2 compared with HIV-1 & dual infections (HIV 1/2) in Mumbai. Indian J Med Res 2010;132:683-9.

9. Drylewicz J, Eholie S, Maiga M, Zannou DM, Sow PS, Ekouevi DK, et al. First-year lymphocyte T $CD4^+$ response to antiretroviral therapy according to the HIV type in the IeDEA West Africa collaboration. AIDS 2010;24(7):1043-50.

10. Ruelle J, Roman F, Vandenbroucke AT, Lambert C, Fransen K, Echahidi F, et al. Transmitted drug resistance, selection of resistance mutations and moderate antiretroviral efficacy in HIV-2: analysis of the HIV-2 Belgium and Luxembourg database. BMC Infect Dis 2008;8:21.

5. Bibliography of included studies

1. Drylewicz J, Matheron S, Lazaro E, Damond F, Bonnet F, Simon F, et al. Comparison of viro-immunological marker changes between HIV-1 and HIV-2-infected patients in France. AIDS 2008;22(4):457-68.

2. Benard A, van Sighem A, Taieb A, Valadas E, Ruelle J, Soriano V, et al. Immunovirological response to triple nucleotide reverse-transcriptase inhibitors and ritonavir-boosted protease inhibitors in treatment-naive HIV-2-infected patients: the ACHI(E)V(2E) Collaboration Study Group. Clinical Infectious Diseases 2011;52(10):1257-66.

3. Harries K, Zachariah R, Manzi M, Firmenich P, Mathela R, Drabo J, et al. Baseline characteristics, response to and outcome of antiretroviral therapy among patients with HIV-1, HIV-2 and dual infection in Burkina Faso. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2010;104(2):154-61.

4. Peterson I, Togun O, de Silva T, Oko F, Rowland-Jones S, Jaye A, et al. Mortality and immunovirological outcomes on antiretroviral therapy in HIV-1 and HIV-2-infected individuals in the Gambia. AIDS 2011;25(17):2167-75.

5. Benard A, Damond F, Campa P, Peytavin G, Descamps D, Lascoux-Combes C, et al. Good response to lopinavir/ritonavir-containing antiretroviral regimens in antiretroviral-naive HIV-2-infected patients. AIDS 2009;23(9):1171-3.

6. Matheron S, Damond F, Benard A, Taieb A, Campa P, Peytavin G, et al. CD4 cell recovery in treated HIV-2-infected adults is lower than expected: results from the French ANRS CO5 HIV-2 cohort. AIDS 2006;20(3):459-62.

7. van der Ende ME, Prins JM, Brinkman K, Keuter M, Veenstra J, Danner SA, et al. Clinical, immunological and virological response to different antiretroviral regimens in a cohort of HIV-2-infected patients. AIDS 2003;17(Suppl 3):S55-S61.

8. Gottlieb GS, Badiane NM, Hawes SE, Fortes L, Toure M, Ndour CT, et al. Emergence of multiclass drug-resistance in HIV-2 in antiretroviral-treated individuals in Senegal: implications for HIV-2 treatment in resource-limited west Africa. Clin Infect Dis 2009;48(4):476-83.

9. Jallow S, Alabi A, Sarge-Njie R, Peterson K, Whittle H, Corrah T, et al. Virological response to highly active antiretroviral therapy in patients infected with human immunodeficiency virus type 2 (HIV-2) and in patients dually infected with HIV-1 and HIV-2 in the Gambia and emergence of drug-resistant variants. J Clin Microbiol 2009;47(7):2200-8.

10. Jallow S, Kaye S, Alabi A, Aveika A, Sarge-Njie R, Sabally S, et al. Virological and immunological response to Combivir and emergence of drug resistance mutations in a cohort of HIV-2 patients in the Gambia. AIDS 2006;20(10):1455-8.

11. Adje-Toure CA, Cheingsong R, Garcia-Lerma JG, Eholie S, Borget MY, Bouchez JM, et al. Antiretroviral therapy in HIV-2-infected patients: changes in plasma viral load, CD4+ cell counts, and drug resistance profiles of patients treated in Abidjan, Côte d'Ivoire. AIDS 2003;17(Suppl 3):S49-S54.

12. Drylewicz J, Eholie S, Maiga M, Zannou DM, Sow PS, Ekouevi DK, et al. First-year lymphocyte T $CD4^+$ response to antiretroviral therapy according to the HIV type in the IeDEA west Africa collaboration. AIDS 2010;24(7):1043-50.

13. Chiara M, Rony Z, Homa M, Bhanumati V, Ladomirska J, Manzi M, et al. Characteristics, immunological response & treatment outcomes of HIV-2 compared with HIV-1 & dual infections (HIV 1/2) in Mumbai. Indian J Med Res 2010;132:683-9.

14. Ruelle J, Roman F, Vandenbroucke AT, Lambert C, Fransen K, Echahidi F, et al. Transmitted drug resistance, selection of resistance mutations and moderate antiretroviral efficacy in HIV-2: analysis of the HIV-2 Belgium and Luxembourg database. BMC Infect Dis. 2008;8:21.

15. Ndour CT, Batista G, Manga NM, Gueye NF, Badiane NM, Fortez L, et al. [Efficacy and tolerance of antiretroviral therapy in HIV-2 infected patients in Dakar: preliminary study]. Med Mal Infect 2006;36(2):111-4.

16. Landman R, Damond F, Gerbe J, Brun-Vezinet F, Yeni P, Matheron S. Immunovirological and therapeutic follow-up of HIV-1/HIV-2-dually seropositive patients. AIDS 2009;23(3):426-8.

17. Peterson K, Ruelle J, Vekemans M, Siegal FP, Deayton JR, Colebunders R. The role of raltegravir in the treatment of HIV-2 infections: evidence from a case series. Antivir Ther 2012;17(6):1097-100.

18. Borget MY, Diallo K, Adje-Toure C, Chorba T, Nkengasong JN. Virologic and immunologic responses to antiretroviral therapy among HIV-1 and HIV-2 dually infected patients: case reports from Abidjan, Côte d'Ivoire. J Clin Virol. 2009;45(1):72-5.

6. Excluded studies with reasons

Reasons for exclusion

- No information on ART (untreated patients)
- Limited data on ART (only the number of patients receiving ART was reported)
- Genotypic analysis without details on ART
- Case report or sample size with fewer than five people receiving ART
- Other reasons (please specify)
- Review of literature
- In vitro study

Excluded studies (after screening the abstracts), with reasons for exclusion

	Reference	Reasons for exclusion
1	Alabi AS, AIDS 2003	No information on ART
2	Albuquerque AS, Clinical Immunology 2007	No information on ART

	Reference	Reasons for exclusion
3	Andersson S, Arch Intern Med 2000	No information on ART
4	Andersson S, Clin Exp Immunol 2005	No information on ART
5	Ariyoshi, Aids 2000	No information on ART
6	Berry N, Aids Res and Human Retr 2002	No information on ART
7	Blaak, JAIDS 2004	No information on ART
8	Brower ET, Chem Biol Drug Des 2008	Review of literature
9	Esbjörnsson J, NEJM 2012	No information on ART
10	Holmgren B, AIDS 2003	No information on ART
11	Holmgren B, Retrovirology 2007	No information on ART
12	Jaffar S, JAIDS 1997	No information on ART
13	Jaffar S, AIDS Res Hum Retroviruses 2005	No information on ART
14	Jallow S, CID 2009	Case report or simple size with fewer than five people receiving ART
15	Koblavi-Deme S, AIDS 2004	No information on ART
16	Maniar JK, Int J STD AIDS 2006	Case report or sample size with fewer than five people receiving ART
17	Mullins C, CID 2004	Limited data on ART with limited response
18	Norrgren H, Int J Infect Dis 2010	No information on ART
19	Ntemgwa ML, Antimicrob Agents Chemother 2009	Review of literature
20	Ntemgwa ML, Antimicrob Agents Chemother 2009	Case report or sample size with fewer than five people receiving ART
21	Parkin N, AIDS 2003	Other reasons
22	Peeters H, Lancet 1992	Other reasons
23	Roquebert B, Journal of Antimicrobial Chemotherapy 2008	In vitro study
24	Ruelle J, AIDS Res Hum Retroviruses 2007	No information on ART
25	Salgado, M, Journal of Clinical Virology 2009	In vitro study
26	Schutten M, NEJM 2000	Limited data on antiretroviral response
27	Smith RA, AIDS 2011	Limited data on antiretroviral response
28	Gottlieb G, PLOS One 2011	Limited data on antiretroviral response
29	Smith RA, PLOS One 2012	Limited data on antiretroviral response
30	Smith, RA JID 2009	Limited data on antiretroviral response
31	Van der Ende E, AIDS 1996	No information on ART
32	Van der Loeff MF, Retrovirology 2010	No information on ART
33	Van Tienen, C, PLOS One 2011	No information on ART
34	Whittle, AIDS 1994	No information on ART
35	Xu L, AIDS Res Hum Retr 2009	Case report with fewer than five people receiving ART
36	Gilliece, HIV Med 2010	Guidelines
37	Peteson, AIDS Research & Treatment 2010	Review of literature
38	New York State HIV Guidelines- NEW: Human Immunodeficiency Virus Type 2 (HIV-2)	Guidelines

	Reference	Reasons for exclusion
39	Campbell-Yesufu, HIV Med 2010	Update on HIV-2

Among 40 full-text articles assessed for HIV-2 systematic review, we excluded 22 manuscripts for the following reasons.

	Reference	Reason for exclusion
1	Armstrong-James D, Antiviral Research 2010	Case report with fewer than five people receiving ART
2	Caixas U, J Antimicrob Chemother	Case report with fewer than five people receiving ART
3	Cavaco-Silva, J Antimicrob Chemother	Limited data on antiretroviral response
4	Clark NM, AIDS 1998	Other reasons
5	Damond F, AIDS 2008	Case report with fewer than five people receiving ART
6	Damond F, Antiviral Therap 2004	Case report with fewer than five people receiving ART
7	Descamps D, J Med Virol 2004	Limited data on antiretroviral response
8	Fonquernie L, Trans R Soc Trop Med Hyg	Case report with fewer than five people receiving ART
9	Garrett N, AIDS 2008	Case report with fewer than five people receiving ART
10	Houston SC, AIDS 2002	Other reasons
11	Martinez-Steele E, AIDS 2007	No information on ART
12	Matheron S, AIDS 2003	Limited data on antiretroviral response
13	Rodes B, AIDS 2006	Case report with fewer than five people receiving ART
14	Rodes B, Antimicrob Agents Chemother 2006	Case report with fewer than five people receiving ART
15	Rodes B, CID 2005	Case report with fewer than five people receiving ART
16	Rodes B, J Clin Microbiol 2000	Limited data on antiretroviral response
17	Roquebert B, AIDS 2008	Case report with fewer than five people receiving ART
18	Schim Van der Loeff, AIDS 2002	No information on ART
19	Smith RA, J Infect 2009	Limited data on antiretroviral response
20	Togun T, AIDS Res Ther 2011	Limited data on antiretroviral response
21	Van der Ende E, JAIDS 2000	Case report with fewer than five people receiving ART
22	Wandeler G, AIDS	Case report with fewer than five people receiving ART