[New 2015]

EPI 4: Antiepileptic medications for adults and children with HIV [New 2015]

SCOPING QUESTION: For adults and children living with HIV, which antiepileptic medications (such as phenobarbital, phenytoin, carbamazepine or valproic acid) produce benefits and/or harms when compared to a placebo or controls?

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BACKGROUND

HIV-positive patients are at an increased risk of seizures through multiple mechanisms, including vulnerability of the central nervous system (CNS) to HIV-associated conditions, such as opportunistic infections, immune dysfunction and metabolic disturbances. Seizure disorders are common in individuals with HIV, with a reported incidence as high as 11%;with many patients requiring antiepileptic medication therapy (Holmberg et al., 1995; Kellinghaus et al., 2008; Wong et al., 1990). In a study of 1345 patients with HIV who were followed at the Southern Alberta Clinic in Canada, 169 (12.6%) were taking antiepileptic medications (Lee et al., 2012).

Antiepileptic medications and antiretroviral (ARV) medications may interact through competition for protein binding, enhanced or reduced liver metabolism and increased viral replication (Kellinghaus et al., 2008). Several older generation antiepileptic medications commonly available in resource-limited regions are inducers of the CYP450 hepatic enzyme system, including phenobarbital, carbamazepine and phenytoin. These medications may reduce levels of ARV medications metabolized by the CYP450 system, including non-nucleotide reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). Additionally, HIV patients may have altered physiologic properties, such as hypoalbuminemia, which significantly increases the unbound fraction of certain antiepileptic medication in the body, including phenytoin and valproic acid (sodium valproate). Alteration of medication levels may lead to medication toxicity or poor virologic and/or seizure control.

Therefore, antiepileptic medication selection must strike a balance between maximizing seizure control, minimizing medication side effects and avoiding exacerbation of underlying medical conditions. In general, the ideal antiepileptic medication in the people living with HIV should avoid hepatic metabolism, should minimize drug-drug interaction, should not be protein-bound and should have a favourable side-effect profile. Given the high incidence of seizures in people with HIV and the increasing use of antiepileptic medications in non-epileptic conditions (including for mood disorders, peripheral neuropathy and headache disorders), it is important to understand the potential adverse interactions between antiepileptic medications and ARVs and to prescribe the safest and most effective medication accordingly.

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The objective of this scoping question is to identify and recommend the best treatment option for HIV-positive people with seizure disorders and to incorporate evidence published since 2009.

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome (PICO)

- **Population:** Adults and children with HIV taking ARVs and antiepileptic medications
- **Interventions:** Standard antiepileptic medications (including phenobarbital, carbamazepine, phenytoin and valproic acid)
- **Comparison:** Placebo, one intervention vs. the other intervention
- **Outcomes:**
    - **Critical** – Seizure recurrence, adverse events, mortality

Search strategy

The following databases were searched to identify relevant systematic reviews and applicable studies: PubMed MeSH, The Cochrane Review Database, MEDLINE PLUS, Web of Science, the WHO Regional Database, the Global Health Library, WHOLIS, PAHO library catalogue, African Index Medicus, AFROLIB, ArabPsycNet, EurasiaHealth, HERDIN NeON, LILACs and African Journals online (AJOL).

The following keywords were used: *HIV, AIDS and antiepileptic drugs, and seizures, epilepsy, or antiepileptic drugs*.

Using a previously published list of ARVs (Birbeck et al., 2012), an additional search was performed between 1996-2014 in the PubMED MeSH, Cochrane Review and MEDLINE PLUS databases including:

- drug interaction AND (antiepileptic OR anticonvulsant OR AED OR [specific AED (valproic acid, phenobarbital, phenytoin and carbamazepine]) AND (antiretroviral OR ARV OR ART OR HAART OR [ARV from AAN/ILAE Table]).

Inclusion and exclusion criteria

Inclusion criteria: All type of studies in humans, patients taking ARVs and antiepileptic medications.

Exclusion criteria: Animal studies, patients not taking ARVs and antiepileptic medications, HIV-positive patients taking multiple antiepileptic medications.

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List of the systematic reviews identified through the search process

- Birbeck GL, French JA, Perucca E, Simpson DM, Fraimow H, George JM, Okulicz JF, Clifford DB, Hachad H, Levy RH (2012). Evidence-based guideline: Antiepileptic drug selection for people with HIV/AIDS. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Ad Hoc Task Force of the Commission on Therapeutic Strategies of the International League Against Epilepsy. Neurology. 78(2):139-145. doi:10.1212/WNL.0b013e31823efcf8.

- Liedtke MD, Lockhart SM, Rathbun RC (2004). Anticonvulsant and antiretroviral interactions. Annals of Pharmacotherapy. 38(3):482–489.

List of nonsystematic reviews identified through the search process

- Romanelli F and Pomeroy C (2003). Concurrent use of antiretrovirals and anticonvulsants in human immunodeficiency virus (HIV) seropositive patients. Current Pharmaceutical Design. 9(18):1433–1439.

- Romanelli F, Jennings HR, Nath A, Ryan M, Berger J (2000). Therapeutic dilemma: the use of anticonvulsants in HIV-positive individuals. Neurology. 54(7):1404–1407.

- Siddiqi O and Birbeck GL (2013). Safe treatment of seizures in the setting of HIV/AIDS. Current Treatment Options in Neurology. 15(4):529-543.

Overview

No reviews (systematic or nonsystematic) have been written on the interaction of antiepileptic medications and antiretroviral medications in children. No studies examine mortality risk in patients on ARVs and antiepileptic medications. There is one open-label, randomized, multiple-dose, pharmacokinetic study in healthy volunteers on the interaction between lopinavir/ritonavir (LPV/RTV) and phenytoin. There is one randomized, open-label, crossover study in adult healthy subjects evaluating the pharmacokinetic interaction of carbamazepine and efavirenz. Given the overall lack of RCTs, we provide a descriptive analysis of the above systematic and nonsystematic reviews and describe other relevant studies that contribute to the evidence-based guidelines.

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PICO Table

Population: Adults and children with HIV and seizure disorders			
Intervention/ Comparison	**Outcomes**	**Systematic reviews**	**Justification for systematic review used**
Phenobarbital	1) Adverse events 2) Seizure recurrence 3) Mortality	1) Birbeck et al. (2012) 2) No data 3) No data	1) One Class III[1] study
Carbamazepine	4) Adverse events 5) Seizure recurrence 6) Mortality	1) Birbeck et al. (2012) 2) No data 3) No data	1) Two class III studies
Phenytoin	1) Adverse events 2) Seizure recurrence 3) Mortality	1) Romanelli et al. (2000) 2) No data 3) No data	1) Two class III studies
Valproic acid	1) Adverse events 2) Seizure recurrence 3) Mortality	1) Birbeck et al. (2012); Liedtke et al. (2004); Siddiqi et al. (2013) 2) No data 3) No data	1) Three class III studies, two class II[2] studies
Antiretroviral therapy (ARVs)	1) Adverse events 2) Seizure recurrence 3) Mortality	1) Birbeck et al. (2012); Liedtke et al. (2004) 2) No data 1) No data	1) 9 Class III studies, 2 Class IV[3] studies
Enzyme inducing antiepileptic medications (EI-AED)- (Carbamazepine, phenytoin, phenobarbital) and PI/NNRTI ARV combinations	1) Adverse events 2) Seizure recurrence 3) Mortality	1) Birbeck et al. (2012); Liedtke et al. (2004); Siddiqi et al. (2013). 2) No data 3) No data	1) 1 class III evidence, 15 class IV studies

[1] Class III controlled study: A controlled trial in a representative population with an independently assessed, objective outcome measure.
[2] Class II study: A controlled trial in a representative population with masked or objective outcome assessment; or a prospective cohort study with masked or objective outcome assessment and relevant baseline characteristics are equivalent across treatment groups and adjusted for in analysis.
[3] Class IV study: Studies not meeting the criteria for Class I, II or II, including consensus or expert opinion.

Narrative description of the studies that went into the analysis

Birbeck GL, French JA, Perucca E, Simpson DM, Fraimow H, George JM, Okulicz JF, Clifford DB, Hachad H, Levy RH (2012). Evidence-based guideline: Antiepileptic drug selection for people with HIV/AIDS. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Ad Hoc Task Force of the Commission on Therapeutic Strategies of the International League Against Epilepsy. Neurology. 78(2):139-145. doi:10.1212/WNL.0b013e31823efcf8.

Birbeck et al. (2012) provide the evidence-based guidelines from the International League against Epilepsy (ILAE) and the American Academy of Neurology (AAN) for antiepileptic medication selection for individuals with HIV. The AAN and the ILAE formed a joint panel to evaluate the literature on concurrent usage of antiepileptic medications and ARVs. From 1950 to 2010, they queried four major databases (MEDLINE, Cochrane Database, Web of Science and EMBASE) and found 4480 articles with potential data, with 68 full articles reviewed. To be included in the study, articles had to report human in vivo data and at least one outcome measure (either pharmacokinetic (PK) or pharmacodynamics) during co-administration of antiepileptic medications and ARVs in comparison with measures during intake of either antiepileptic medications or ARVs. For the purpose of characterizing a PK medication interaction, patients with the disease of interest and healthy volunteers were considered to be potentially representative populations. PK crossover studies were considered as equivalent to a prospective matched cohort with an objective outcome (serum concentration); thus, meeting criteria for Class II. There were 31 articles identified. There was no Class I evidence found on review. There were five articles rated Class II and eight articles rated Class III. Two additional articles described data in multiple cohorts, of which one cohort in each article produced Class II evidence and the others produced Class III evidence. Detailed information on the design, sample size, methods, limitations and results of the studies included in the Birbeck et al. (2012) review can be found in Table 1 below.

Table 1. Additional details on the articles included in the Birbeck et al. (2012) review

Reference	Design	Sample size	Comparison methods	Limitations	Results
Lertora JJ et al. (1994). Pharmacokinetic interaction between zidovudine and valproic acid in patients infected with human immunodeficiency virus. Clinical Pharmacology and Therapeutics.56:272–278.	Prospective cohort study of six patients ARV naïve, started on zidovudine and valproic acid	N=6; HIV positive, started on zidovudine (ART naïve) and valproic acid	Quantitative analysis of zidovudine and valproic acid concentrations, PK analysis	Sample size	The mean AUC[i] for zidovudine increased significantly, almost two fold after valproic acid co-administration, indicating that valproic acid altered the disposition of zidovudine.

Okulicz JF et al. (2011). Virologic outcomes of HAART with concurrent use of cytochrome P450 enzyme-inducing antiepileptics: a retrospective case control study. AIDS Research and Therapy.8:18.	Retrospective case control study	N=19; 19 participants were treated concurrently with EI-AEDs[ii] and HAART[iii], with 12, 6, and 1 participants taking phenytoin, carbamazepine, and phenobarbital for the first HAART/EI-AED overlap period	Patients taking non-enzyme inducing antiepileptic medications and ARVs (n=85, 82 received gabapentin, 2 pregabalin, and 1 leviteracetam); non-AED, n=190)	Sample size in EI-AED; differing proportions of seizure disorders and neuropathic pain in the two groups, unmeasured medication doses and adherence, HIV medication resistance and other uncharacterized variables unique to patients with seizure disorders or neuropathic pain.	Comparison of EI-AEDs vs. NEI-AEDs[iv] and non-AED[v] control groups combined with HAART showed worse virologic outcomes in the EI-AED group.
Bates DE, Herman RJ (2006). Carbamazepine toxicity induced by lopinavir/ritonavir and nelfinavir. Annals of Pharmacotherapy.40:1190 – 1195.	Case report	N=1	None	Case report	Adverse effects of excessive drowsiness secondary to carbamazepine when an antiretroviral regimen containing LPV/RTV was introduced. The carbamazepine serum concentration increased 46%. Subsequently, the patient developed a possible adverse skin reaction to his ARVs and was hospitalized. The protease inhibitor was changed to nelfinavir. Within 3 days, the patient again developed excessive drowsiness and became unsteady on his feet. This time, the carbamazepine serum concentration had increased by 53%. In both instances, the carbamazepine dosage was decreased by 33%, which resulted in resolution of symptoms.
Bonora S et al. (2007). Clinically significant drug interaction between tipranavir-ritonavir and phenobarbital in an HIV-infected subject. Clinical Infectious Diseases,45:1654 –1655.	Case report	N=1	None	Case report	Concomitant administration of TPV/RTV and phenobarbital led to a 50% decrease of phenobarbital plasma levels, requiring 50% increase in the daily phenobarbital dose.

Burman W, Orr L (2000). Carbamazepine toxicity after starting combination antiretroviral therapy including ritonavir and efavirenz. AIDS.14:2793–2794.	Case report	N=1	None	Case report	Carbamazepine toxicity after starting an ARV treatment regimen including ritonavir. A dose reduction from 600 to 100 mg was required to achieve a therapeutic carbamazepine concentration.
DiCenzo R et al. (2004). Effects of valproic acid coadministration on plasma efavirenz and lopinavir concentrations in human immunodeficiency virus-infected adults. Antimicrobial Agents and Chemotherapy.48:4328–4331.	Prospective PK cohort study. Three groups of HIV-positive subjects: a group receiving lopinavir-ritonavir +/- VPA[vi], a group receiving efavirenz +/- VPA, and a VPA control group that received neither lopinavir-ritonavir nor efavirenz.	The numbers of subjects included in the efavirenz plus NRTI[vii], lopinavir-ritonavir plus NRTI, and VPA without efavirenz or lopinavir groups were 11, 11 and 12, respectively.	Efavirenz/Lopinavir-Ritonavir without VPA	PK parameters in those with combined nucleoside reverse transcriptase inhibitors alone or who had discontinued ARV therapy.	VPA does not appear to alter plasma efavirenz concentrations. Efavirenz administered with VPA is bioequivalent to efavirenz administered alone. Administration of lopinavir-ritonavir alone does not appear to be equivalent to administration of lopinavir-ritonavir with VPA. These results suggest that plasma lopinavir concentrations may be higher during VPA co-administration. The GMR (90% CI) of the AUC0-8s after administration of the dose of lopinavir with and without VPA co-administration was 1.38 (0.98, 1.94) and six of the eight subjects achieved higher plasma lopinavir concentrations during VPA co-administration. The lopinavir *C*max, minimum observed concentration, *T*max and half-life were not significantly different during VPA administration ($P > 0.10$). Neither administration of efavirenz nor that of LPV/RTV appeared to affect VPA concentrations measured just before ($C0$) or 8 hours after administration of the dose.

Honda M et al. (1999). A generalized seizure following initiation of nelfinavir in a patient with human immunodeficiency virus type 1 infection, suspected due to interaction between nelfinavir and phenytoin. Intern Med.38:302–303.	Case report	N=1	None	Case report	A generalized seizure followed initiation of nelfinavir in a patient with HIV type 1 infection, suspected due to interaction between nelfinavir and phenytoin
Hugen PW et al. (2000). Carbamazepine–indinavir interaction causes antiretroviral therapy failure. Annals of Pharmacotherapy.34:465– 470.	Case report	N=1	None	Case report	A low dose of carbamazepine (200 mg/d) and the usual dose of indinavir (800 mg q8h) in the patient resulted in carbamazepine concentrations within the therapeutic range for epilepsy treatment; indinavir concentrations dropped substantially. The virologic, resistance and plasma medication concentration data, as well as the chronology of events, are highly indicative of antiretroviral treatment failure due to the interaction between carbamazepine and indinavir.
Kato Y et al. (2000). Potential interaction between ritonavir and carbamazepine. Pharmacotherapy.20:851– 854.	Case report	N=1	None	Case report	Ritonavir (RTV) and carbamazepine (CBZ), were administered concurrently to a patient who had human immunodeficiency virus infection and epilepsy. The combination resulted in elevated serum concentrations of CBZ, with accompanying vomiting, vertigo and transient liver dysfunction. After discontinuing RTV and reducing the dosage of CBZ, the serum concentration of

					CBZ returned to the optimal range, symptoms subsided and liver function returned to baseline.
Lim ML et al. A two-way drug interaction between lopinavir/ritonavir and phenytoin. In: Proceedings from the 10th Conference on Retroviruses and Opportunistic Infections; Feb 10–14, 2003; Boston, MA. Abstract 535.	Open label, randomized, multiple-dose, PK study in healthy volunteers	N=24; Subjects in arm A (n = 12) received LPV/RTV 400/100 mg twice daily (BID) (days 1–10), followed by LPV/RTV 400/100 mg BID + PHT 300 mg once daily (QD) (days 11–22). Arm B (n = 12) received PHT 300 mg QD (days 1–11), followed by PHT 300 mg QD + LPV/RTV 400/100 mg BID (days 12–23).	PK of LPV/RTV alone	Sample size, PK analysis with no clinical correlation	A significant two-way medication interaction between LPV/RTV and PHT. Concentrations of LPV and RTV were decreased by the addition of PHT and concentrations of PHT were decreased by the addition of LPV/RTV. Neither *CYP3A*, *2C9/19*, nor *MDR-1* genotype appeared to be predictive of the interaction, although the study was not adequately powered for these comparisons.
Sheehan NL et al. (2006). Possible interaction between lopinavir/ritonavir and valproic acid exacerbates bipolar disorder. Annals of Pharmacotherapy.40:147–150.	Case report	N=1	None	Case report	Patient with bipolar disorder and HIV initiated treatment with LPV/RTV, zidovudine and lamivudine. Prior to beginning therapy with these ARVs, he was receiving VPA 250 mg 3 times daily, with his most recent VPA concentration measured at 495 µmol/L. Twenty-one days after starting ARV treatment, he became increasingly manic. His VPA concentration at admission was 238 µmol/L, a 48% decrease. The daily VPA dose was increased to 1500 mg, and olanzapine was introduced. The VPA concentration following this dose escalation was 392 µmol/L and the patient improved clinically.

Conclusions and recommendations from Birbeck et al. (2012)

- Phenytoin possibly reduces lopinavir and ritonavir levels by about 30%. Patients receiving phenytoin may require a lopinavir/ritonavir dosage increase of about 50% to maintain unchanged serum concentrations.
- Valproic acid possibly increases zidovudine exposure. Patients receiving valproic acid may require a zidovudine dosage reduction to maintain unchanged serum zidovudine concentrations
- Valproic acid possibly has no effect on efavirenz exposure. Co-administration of valproic acid and efavirenz may not require efavirenz dosage adjustment
  Co-administration of HAART containing a PI or NNRTI and an EI-AED possibly results in higher virologic failure rates. It may be important to avoid AEDs in people on ARV regimens that include PIs or NNRTIs, as PK interactions may result in virologic failure, which has clinical implications for disease progression and development of ARV resistance. If such regimens are required for seizure control, patients may be monitored through PK assessments to ensure efficacy of the ARV regimen

Liedtke MD, Lockhart SM, Rathbun RC (2004). Anticonvulsant and antiretroviral interactions. Annals of Pharmacotherapy.38(3):482–489.

Liedtke et al. (2004) conducted a systematic review to evaluate the clinical significance of interactions between anti-epileptic and ARV agents and provide recommendations regarding their concurrent use. A PubMED search from 1966 to April 2003 was conducted using individual anti-epileptic and ARV medication names and the following key search terms: *anticonvulsant, antiepileptic, antiretroviral, protease inhibitor, and pharmacokinetic*. Abstracts from scientific meetings that pertained to medication interactions were manually reviewed. All articles identified by the PubMED search were examined. Articles and abstracts from scientific meetings with relevant information were included.

Carbamazepine:
Three cases are described of patients receiving carbamazepine with PI/NNRTI with subsequent carbamazepine toxicity, including symptoms of intractable vomiting and vertigo. In patients receiving concurrent ritonavir and carbamazepine, there was a two to threefold increase in carbamazepine concentration resulting in clinical toxicity. When carbamazepine and indinavir concurrent therapy was used, there was a loss of viral suppression. Both ritonavir and nelfinavir induce CYP2C9/19 and can increase the metabolism of phenytoin.

Phenytoin:
A pharmacokinetic study in 28 healthy subjects was performed to observe interactions between phenytoin and nelfinavir. Patients were given either phenytoin 300 mg daily or nelfinavir 1250 mg twice daily for 7 days, followed by 7 days of co-administration. The investigators observed a 20–40% decrease in the phenytoin AUC with the addition of nelfinavir. There was no observed decrease in the nelfinavir AUC, but there was a 20% reduction in the AUC of the active M8 metabolite of nelfinavir. One patient with concurrent ritonavir and phenytoin had a 30% reduction in phenytoin serum concentration, while there was no change in another patient on the same combination.

Phenobarbital:
Phenobarbital is a potent inducer of CYP3A4, as well as CYP1A2, 2B6, 2C8 and 2C9/19; however, there is limited data concerning phenobarbital and ARV interactions.

Valproic acid:
There have been reports that valproic acid can impair zidovudine metabolism by inhibiting glucuronidation. A twofold increase in zidovudine AUC has been reported with the addition of valproic acid.

Lamotrigine:
Two case reports of second-generation AEDs and ARVs were included, which showed no CYP450 involvement. Lamotrigine was decreased in a patient receiving lamotrigine and ritonavir. A report of lamotrigine use with lopinavir/ritonavir, lamivudine, and stavudine resulted in a decline in viral load after two months of therapy and seizure freedom.

Detailed information on the design, sample size, methods, limitations and results of the studies included in the Liedtke et al. (2004) review can be found in Table 2 below.

Table 2. Additional details on the articles included in the Liedtke et al. (2004) review

Reference	Design	Sample size	Comparison methods	Limitations	Results
Shelton MR et al. (2000). Evaluation of the pharmacokinetic interactions between phenytoin and nelfinavir in healthy volunteers at steady state (abstract 426). Presented at: 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, September 17–20, 2000.	Cohort study, PK study	28	None	PK, with no clinical correlates, limited information with abstract	Phenytoin concentrations were reduced by nelfinavir, with a decrease in the AUC of approximately 30%. Nelfinavir parent medication levels were unaffected by phenytoin, whereas the active M8 metabolite was significantly decreased.
Burman W and Orr L (2000). Carbamazepine toxicity after starting combination antiretroviral therapy including ritonavir and efavirenz. AIDS.14:2793-4.	Case report	N=1	None		Clinical toxicity was noted in a patient whose ARV therapy was changed from zidovudine, lamivudine and indinavir to a regimen of ritonavir,

					saquinavir and efavirenz. Carbamazepine serum concentrations increased by threefold to 20.4 µg/mL. Ultimately, the patient required an 83% reduction in her carbamazepine dose, from 600 to 100 mg/day, before symptoms resolved and the plasma carbamazepine concentrations stabilized within the therapeutic range (4.0–12.0 µg/mL).
Dato Y et al. (2000). Potential interaction between ritonavir and carbamazepine. Pharmacotherapy.20:851-854.	Case report	N=1	None	Case report	Ritonavir (RTV) and carbamazepine (CBZ) were administered concurrently to a patient who had human immunodeficiency virus infection and epilepsy. The combination resulted in elevated serum concentrations of CBZ, with accompanying vomiting, vertigo and transient liver dysfunction. After discontinuing RTV and reducing the dosage of CBZ, the serum concentration of CBZ returned to the optimal range, symptoms subsided and liver function returned to baseline.
Hugen PW et al. (2000). Carbamazepine–indinavir interaction causes antiretroviral therapy failure. Annals of Pharmacotherapy.34:465-470.	Case report	N=1	None	Case report	A low dose of carbamazepine (200 mg/d) and the usual dose of indinavir (800 mg q8h) in the patient resulted in carbamazepine concentrations within the therapeutic range for epilepsy treatment; indinavir concentrations

					dropped substantially. The virologic, resistance and plasma medication concentration data, as well as the chronology of events, are highly indicative of antiretroviral treatment failure due to the interaction between carbamazepine and indinavir.
Lim M et al. (2003). A two-way drug interaction between lopinavir/ritonavir and phenytoin (abstract 535). Presented at: 10th Conference on Retroviruses and Opportunistic Infections, Boston, February 10–14, 2003.	Open label, randomized, multiple-dose, PK study in healthy volunteers	N=24; Subjects in arm A (n = 12) received LPV/RTV 400/100 mg twice daily (BID) (days 1–10), followed by LPV/RTV 400/100 mg BID + PHT 300 mg once daily (QD) (days 11–22). Arm B (n = 12) received PHT 300 mg QD (days 1–11), followed by PHT 300 mg QD + LPV/RTV 400/100 mg BID (days 12–23).	PK of LPV/RTV alone	Sample size, PK analysis with no clinical correlation	A significant two-way medication interaction between LPV/RTV and PHT was observed. Concentrations of LPV and RTV were decreased by the addition of PHT and concentrations of PHT were decreased by the addition of LPV/RTV. Neither *CYP3A*, *2C9/19*, nor *MDR-1* genotype appeared to be predictive of the interaction, although the study was not adequately powered for these comparisons.
Lertora J et al. (1994). Pharmacokinetic interaction between zidovudine and valproic acid in patients with human immunodeficiency virus. Clinical Pharmacology and Therapeutics. 56:272-278.	Prospective cohort study of 6 patients ARV naïve, started on zidouvudine and VPA	N=6; HIV positive, started on zidovudine (ART naïve) and VPA	Quantitative analysis of zidovudine and VPA concentrations, PK analysis	Sample size	The mean AUC for zidovudine increased significantly, almost two fold after VPA co-administration, indicating that VPA altered the disposition of zidovudine.

Conclusions and recommendations from Liedtke et al. (2004)

- Limited data exist regarding interactions between anti-epileptic and ARV agents.
- Valproic acid and newer anti-epileptic agents may provide useful alternatives to first-generation agents. When possible, consideration should be given to substituting valproic acid for the anti-epileptic currently being used due to minimal medication– medication interactions and the

availability of established targets for serum concentrations. Among the second-generation anti-epileptics, levetiracetam, gabapentin and lamotrigine do not alter metabolism of other medications through CYP450 and appear the most promising for patients on ARV therapy who require adjunctive therapy for partial seizures. Therapeutic and toxic ranges are not well established for newer anti-epileptics.

- In some patients, lamotrigine monotherapy is sufficient to control partial seizures and may represent a useful alternative when standard anti-epileptics cannot be utilized. Ritonavir may lower lamotrigine plasma concentrations, which should be considered when these agents are used concurrently.
- In situations where using EI-AEDs are unavoidable, clinicians need to be diligent when monitoring for anti-epileptic–ARV interactions because of the potential for toxicity, loss of seizure control and incomplete viral suppression.
- If it is necessary to use protease inhibitor–based ARV therapy in combination with traditional anti-epileptics, regimens that include ritonavir to enhance the PK profile (or "boost") should be utilized. Concomitant use of ritonavir with protease inhibitors has been shown to offset the increased clearance associated with known enzyme inducers (e.g., efavirenz). On the basis of experience with protease inhibitor and NNRTI interactions, a ritonavir dose of 200 mg is preferable to using lower doses (e.g., 50–100 mg) in the absence of specific PK data with anti-epileptics.
- Alternatively, when using lopinavir/ritonavir the addition of another lopinavir/ ritonavir capsule to each dose (i.e., lopinavir 533 mg/ritonavir 133 mg twice daily) may be sufficient to ensure adequate lopinavir serum concentrations.

Siddiqi O and Birbeck GL (2013). Safe treatment of seizures in the setting of HIV/AIDS. Current Treatment Options in Neurology. 15(4):529-543.

Siddiqi and Birbeck (2013) conducted a non-systematic review on the diagnosis and treatment of new onset seizures in patients with HIV. For patients treated with PIs and NNRTIs, studies recommend avoiding EI-AEDs, including phenytoin, phenobarbital and carbamazepine.

Carbamazepine and phenytoin:

Carbamazepine and phenytoin demonstrated a reduced half-life of the NNRTI nevirapine. Another study demonstrated that carbamazepine reduces the serum concentration of the NNRTI efavirenz. A natural history study of HIV-positive US military personnel demonstrated a greater risk of virologic failure in patients taking EI-AEDs and HAART, compared with patients taking not EI-AEDs and HAART.

Valproic acid:

While previous in vitro studies have shown valproic acid in HIV-positive patients to stimulate HIV replication, in vivo studies have not shown this.

Detailed information on the design, sample size, methods, limitations and results of the studies included in the Siddiq and Birbeck (2012) review can be found in Table 3 below.

Table 3. Additional details on the articles included in the Siddiqi and Birbeck (2012) review

Reference	Design	Sample size and demographics	Comparison methods	Limitations	Results
Ji P et al. (2008). Pharmacokinetic interaction between efavirenz and carbamazepine after multiple-dose administration in healthy subjects. Journal of Clinical Pharmacology.48(8):948–956.	Randomized, open-label, crossover study in adult healthy subjects to evaluate the effect of 400 mg carbamazepine on the pharmacokinetics of 600 mg efavirenz (arm 1) and the effect of 600mg efavirenz on the pharmacokinetics of 400mg carbamazepine (arm 2).	Thirty-six healthy adult subjects N=36 healthy subjects (25 men and 11 women)	Efavirenz alone and carbamazepine alone	Sample size, no clinical correlation	Co-administration of carbamazepine with efavirenz significantly reduced the exposure of efavirenz (geometric mean ratios [90% confidence interval]: area of plasma concentration-time curve during the dosing interval of 24 hours [AUCτ], 0.64 [0.60-0.68]; maximum plasma concentration [Cmax], 0.79 [0.74, 0.85]) and carbamazepine (AUCτ, 0.73 [0.67-0.80]; Cmax, 0.80 [0.76, 0.85]) but had minimal impact on the exposure of carbamazepine-10,11-epoxide (AUCτ, 0.99 [0.85-1.15]; Cmax, 1.05 [0.91, 1.22]). In summary, a 2-way pharmacokinetic interaction between efavirenz and carbamazepine was demonstrated in this study.
Okulicz JF et al. (2011). Virologic outcomes of HAART with concurrent use of cytochrome P450 enzyme-inducing antiepileptics: a retrospective case control study. AIDS Research and Therapy.8:18.	Retrospective case control study	N=19; 19 participants were treated concurrently with EI-AEDs and HAART, with 12, 6, and 1 taking phenytoin, carbamazepine, and phenobarbital for the first HAART/EI-AED overlap period	Patients taking nonenzyme inducing antiepileptic medications and ARVs (n=85, 82 received gabapentin, 2 pregabalin, and 1 leviteracetam); non-AED, n=190)	Sample size in EI-AED; differing proportions of seizure disorders and neuropathic pain in the two groups, unmeasured medication doses and adherence, HIV medication resistance, and other uncharacterized variables unique to patients with seizure disorders or neuropathic pain.	Comparison of EI-AEDs vs. NEI-AEDs and non-AED control groups combined with HAART showed worse virologic outcomes in the EI-AED group.

Sagot-Lerolle N et al. (2008). Prolonged valproic acid treatment does not reduce the size of latent HIV reservoir. AIDS.22(10):1125–1129.	Single center pilot study	N=23; N=11 taking VPA, N=13 age matched controls	Controls not on VPA	Sample size	Total and integrated HIV DNA was logarithmically more abundant than cells carrying replication-competent virus, but there was no significant difference in these three parameters between the two groups of matched patients.
Yacoob Y et al. (2011). Valproic acid and highly active antiretroviral therapy in HIV positive patients who develop new onset seizures. Seizure.20(1):80–82.	Case cohort	N=8	None	Sample size	VPA is shown to be safe and effective in patients on ARVs
DiCenzo R et al. (2004). Effects of valproic acid coadministration on plasma efavirenz and lopinavir concentrations in human immunodeficiency virus-infected adults. Antimicrobial Agents and Chemotherapy.48(11):4328–4331.	Prospective PK cohort study. Three groups of HIV-positive subjects: a group receiving lopinavir-ritonavir +/- VPA, a group receiving efavirenz +/- VPA and a VPA control group that received neither lopinavir-ritonavir nor efavirenz.	The numbers of subjects included in the efavirenz plus NRTI, lopinavir-ritonavir plus NRTI and VPA without efavirenz or lopinavir groups were 11, 11 and 12, respectively.	Efavirenz/Lopinavir-Ritonavir without VPA	PK parameters in those with combined nucleoside reverse transcriptase inhibitors alone or had discontinued ARV therapy.	VPA does not appear to alter plasma efavirenz concentrations. Efavirenz administered with VPA is bioequivalent to efavirenz administered alone. Administration of lopinavir-ritonavir alone does not appear to be equivalent to administration of lopinavir-ritonavir with VPA. Our results suggest that plasma lopinavir concentrations may be higher during VPA co-administration. The GMR (90% CI) of the AUC0-8s after administration of the dose of lopinavir with and without VPA co-administration was 1.38 (0.98, 1.94) and six of the eight subjects achieved higher plasma lopinavir concentrations during VPA co-administration. The lopinavir *C*max, minimum observed concentration, *T*max and half-life were not significantly different during VPA administration ($P > 0.10$). Neither administration of efavirenz nor that of lopinavir-ritonavir appeared to effect VPA concentrations measured just before ($C0$) or 8 hours after administration of the dose.
Lertora JJ et al. (1994). Pharmacokinetic interaction between zidovudine and valproic acid in patients	Prospective cohort study of 6 patients ARV naïve, started on zidouvudine and VPA	N=6; HIV positive, started on Zidovudine (ART naïve) and VPA	Quantitative analysis of Zidovudine and VPA concentrations, PK analysis	Sample size	The mean AUC for zidovudine-increased almost two fold after VPA co-administration, indicating that VPA altered the disposition of zidovudine.

infected with human immunodeficiency virus. Clinical Pharmacology and Therapy.56(3):272–278.					

Conclusions and recommendations from Siddiqi et al. (2013)

- When available, the recommended AEDs are levetiracetam followed by lacosamide, gabapentin and pregabalin. All four are metabolized in the kidney and do not interact with any AEDs or ARVs.
- Levetiracetam and lacosamide can be administered orally or intravenously (though intravenous formulation is uncommon), but levetiracetam has the additional benefit of being more moderately priced and does not need to be avoided in patients with second and third degree atrioventricular block, which is the case with lacosamide.
- Gabapentin and pregabalin can be administered only orally and the costs range from moderate to expensive.
- When newer AEDs are not available, valproic acid is a reasonable choice as it will not cause a drug-drug interaction that results in ARV failure. It is an enzyme-inhibiting agent and has demonstrated increased serum of levels of the protease inhibitor lopinavir/ritonavir and the nucleoside reverse transcriptase inhibitor zidovudine when co-administered. Thus, it should be used with caution and may require dose adjustments, particularly with the PIs and NNRTIs in order to avoid medication toxicity.

Romanelli F and Pomeroy C (2003). Concurrent use of antiretrovirals and anticonvulsants in human immunodeficiency virus (HIV) seropositive patients. Current Pharmaceutical Design.9(18):1433–1439.

Romanelli and Pomeroy (2003) conducted a non-systematic literature review of ARV and AED use in HIV-positive patients. The authors did not include the methods of this search, key terms, number of articles found or the review process of which articles were included. Six studies indicated the correlation of hypoalbuminemia increasing the free concentrations of highly protein-bound AEDs, including phenytoin, carbamazepine, clonazepam and diazepam. ARVs examined included delavirdine, efavirenz, saquinavir ritonavir, nelfinavir, lopinavir and amprenavir. Three AIDS patients with hypoalbuminaemia had elevated serum concentrations of both phenytoin and valproic acid, when compared to patients taking these anti-epileptics with AIDS or hypoalbuminaemia.

HIV hypergammaglobulinemia was noted in four cases to predispose patients to potentially life threatening hypersensitivity reactions. One of these reported that 14% of HIV-positive patients receiving phenytoin had hypersensitivity reactions, including Stevens – Johnson syndrome. Three cases of interaction of PIs with EI-AED are discussed.

Five studies included the possible correlation of valproic acid to stimulate in vitro HIV and cytomegalovirus (CMV) replication. However, in one

included study, six of nine patients followed for 1–13 weeks did not show an increase in viral loads.

Detailed information on the design, sample size, methods, limitations and results of the studies included in the Romanelli and Pomeroy (2003) non-systematic review can be found in Table 4 below.

Table 4. Additional details on the articles included in the Romanelli and Pomeroy (2003) review

Reference	Design	Sample size	Comparison methods	Limitations	Results
Toler SM et al. (1990). Severe phenytoin intoxication as a result of altered protein binding in AIDS. Annals of Pharmacotherapy. 24:698-700.	Case report	N=1	None	Case report	HIV-positive patient on ARVs showed markedly elevated free phenytoin concentrations.
Burger DM et al. (1994). Therapeutic drug monitoring of phenytoin in patients with the acquired immunodeficiency syndrome. Therapeutic Drug Monitoring.16:616-620.	Case cohort	N=21	HIV-negative patient samples	Sample size, no clinical correlation	Total phenytoin concentrations were significantly lower in patients with AIDS than in the reference population. Measurement of free phenytoin concentrations demonstrated that the fraction of unbound medication was increased in patients with AIDS.
Dasgupta A, McLemore JL (1998). Elevated free phenytoin and free valproic acid concentrations in sera of patients infected with human immunodeficiency virus. Therapeutic Drug Monitoring, 20:63-67.	Retrospective cohort	Unclear number	HIV-negative patient samples	Unknown sample size	The concentration of free phenytoin and free VPA were significantly elevated in patients with HIV (mean = 2.52, SD = 0.11 µg/ml for phenytoin; mean = 41.5, SD = 1.5µg/ml for valproate) compared to controls (mean = 1.50, SD = 0.0 7µg/ml for phenytoin; mean = 19.9, SD = 0.5 µg/ml for valproate). The concentrations of both free phenytoin and VPA were further elevated in patients prepared in the HIV pool who were receiving bactrim (mean= 2.81, SD = 0.09 µg/ml for phenytoin; mean = 44.0, SD = 1.1 µg/ml for valproate), but when normal serum pool was supplemented with 4.4 mg/dl of bactrim (concentration of bactrim in HIV pool) and supplemented with the same concentration of phenytoin or VPA, the observed free concentrations were much lower (mean = 1.65, SD = 0.05 µg/ml for phenytoin; mean = 26.1, SD = 1.4 µg/ml for valproate).

Hugen PWH et al. (2000). Carbamazepine indinavir interaction causes antiretroviral therapy failure. Annals of Pharmacotherapy.34:465-470	Case report	N=1	None	Case report	Case of a 48-year old HIV-positive man who was receiving a standard regimen that consisted of zidovudine, lamivudine and indinavir (800mg, every 8 hours) and who had an undetectable viral load (<400 copies/ml). One month following the last confirmed viral load, the patient developed post-herpetic neuralgia and was prescribed carbamazepine 200 mg/day. During carbamazepine therapy, indinavir concentrations decreased substantially and the viral load rose to 6000 copies/ml.
Kato Y et al. (2000). Potential interaction between ritonavir and carbamazepine. Pharmacotherapy.20:851-854	Case report	N=1	None	Case report	Ritonavir (RTV) and carbamazepine (CBZ) were administered concurrently to a patient who had HIV and epilepsy. The combination resulted in elevated serum concentrations of CBZ, with accompanying vomiting, vertigo and transient liver dysfunction. After discontinuing RTV and reducing the dosage of CBZ, the serum concentration of CBZ returned to the optimal range, symptoms subsided and liver function returned to baseline.

Conclusions and recommendations from Romanelli and Pomeroy (2003)

- Anti-epileptics, such as gabapentin or tiagabine that are minimally metabolized by the CYP450 system, may be the best alternative for avoiding interactions involving enzyme inhibition or induction.
- Anti-epileptics with lower affinities for albumin, such as gabapentin or topiramate, theoretically pose less risk for displacement when combined with highly-bound agents.
- Although highly-bound, tiagabine does not appear to pose a significant risk for displacement.
- Unless benefits outweigh risks, it is advisable to avoid the use of valproic acid in HIV-positive patients until more conclusive studies are conducted.

Romanelli F, Jennings HR, Nath A, Ryan M, Berger J (2000). Therapeutic dilemma: the use of anticonvulsants in HIV-positive individuals. Neurology.54(7):1404–1407.

In this non-systematic review, Romanelli et al. (2000) discuss medication-disease interactions, drug-drug interactions and the effect of AEDs on viral replication. Hypoalbuminemia seen in HIV-positive patients may alter free phenytoin and valproic acid levels and affects dosing, warranting vigilant

monitoring (e.g., with unbound phenytoin levels) to avoid toxicity. One study describes a patient receiving phenytoin 250 mg/day who developed markedly elevated free phenytoin concentrations as a result of AIDS-associated hypoalbuminemia.

Secondary to hypergammaglobulinemia, many HIV-positive patients are at an increased risk of developing hypersensitivity reactions. Specifically, it has been identified that as many as 14% of HIV-positive patients receiving phenytoin therapy develop hypersensitivity reactions, such as Stevens–Johnson syndrome. Comparatively, the incidence of allergic reactions in HIV-negative patients is less. In addition, the rate of medication hypersensitivity reactions with trimethoprim/sulfamethoxazole in HIV-positive individuals is 10 times greater than in the normal population. This may lead to increased free medication levels, which in turn increases side effects and toxicity.

Valproic acid

Valproic acid has also been shown to stimulate the viral replication of HIV through the reduction of intracellular levels of glutathione. Valproic acid has also been reported to stimulate CMV replication.

Conclusion and recommendations from Romanelli et al. (2000)

- In patients receiving AEDs and ARVs, the authors suggest careful monitoring of viral load, disease progression and AED serum levels.

Overall methodological limitations

- Paucity of RCTs or good quality observational studies in individuals with HIV on ARVS and antiepileptic medications.
- The lack of studies on children.

Overall narrative conclusion

Seizures are a cause of significant morbidity and mortality in HIV-positive patients and should be managed with AEDs that are safe and effective. In HIV-positive patients on ARVs, the optimal AED must minimize the risk of drug-drug interactions and the effects on HIV viral load suppression. The optimal AED in those patients on ARVs avoids hepatic metabolism, minimizes drug-drug interaction, is not protein bound and has a favourable side-effect profile.

Evidence-based quality assessment of the studies that were considered in the analysis

[New 2015]

Table 5. Evidence of old generation AEDs (including phenobarbital, carbamazepine, phenytoin, valproic acid) interaction with ARVs

Reference	Design	Outcome	Indirectness	Other limitations	Quality
Phenobarbital					
L'Homme RF, Dijkema T, van der Ven AJ, Burger DM (2006). Brief report: enzyme inducers reduce elimination half-life after a single dose of nevirapine in healthy women. J Acquir Immune Defic Syndr.43:193-196	Case series	No change in mean nevirapine half-life with single 200 mg phenobarbital dose.	Sample was of healthy women	Sample size, fixed, one-time dose of AED, only PK analysis	VERY POOR
Carbamazepine					
Ji P, Damle B, Xie J, Unger SE, Grasela DM, Kaul S (2008). Pharmacokinetic interaction between efavirenz and carbamazepine after multiple- dose administration in healthy subjects. J Clin Pharmacol.48:948-956.	Randomized, open label crossover	Carbamazepine reduced efavirenz area under the curve by 36% (90% CI 32% to 40%), as compared with efavirenz alone.	Sample was of healthy participants	Sample size, number of dropouts	POOR
L'Homme RF, Dijkema T, van der Ven AJ, Burger DM (2006). Brief report: enzyme inducers reduce elimination half-life after a single dose of nevirapine in healthy women. J Acquir Immune Defic Syndr.43:193-196	Case series	Mean half-life of nevirapine (single 200-mg dose) was reduced after a single 400-mg dose of carbamazepine (from 52 to 33 hours, p = 0.021), which corresponds to a median decrease of 18.8 hours (range 15.6 –38).	Sample was of healthy women	Sample size, fixed, one time dose	VERY POOR
L'Homme RF, Dijkema T, van der Ven AJ, Burger DM (2006). Brief report: enzyme inducers reduce elimination half-life after a single dose of nevirapine in healthy women. J Acquir Immune Defic Syndr.43:193-196	Case series	Mean nevirapine half-life was reduced after phenytoin treatment 184 mg/day for either 3 days (from 46–27 h, p = 0.021) or 7 days (from 55–34 h, p = 0.021). There was no significant change in mean nevirapine half-life after a single 184-mg phenytoin dose.	Sample was of healthy women	Sample size, short treatment duration, low dose of phenytoin used	VERY POOR
Toler SM et al. (1990). Severe phenytoin intoxication as a result of altered protein binding in AIDS. Annals of Pharmacotherapy.24: 698-700	Case report	HIV-positive patient on ARVs showed markedly elevated free phenytoin concentrations.	Case report	Case report	VERY POOR
Dasgupta A and McLemore JL (1998). Elevated free phenytoin and free valproic acid concentrations in sera of patients infected with human immunodeficiency virus. Therapeutic Drug Monitoring.20:63-7	Retrospective cohort	The concentration of free phenytoin and free VPA were significantly elevated in patients with HIV (mean = 2.52, SD = 0.11 µg/ml for phenytoin; mean = 41.5, SD = 1.5µg/ml for valproate) compared to controls (mean = 1.50, SD = 0.0 7µg/ml for phenytoin; mean = 19.9, SD = 0.5 µg/ml for valproate). The concentrations of both free phenytoin	Unknown sample size	Case series	POOR

Reference	Design	Outcome	Indirectness	Other limitations	Quality
		and VPA were further elevated in patients prepared in the HIV pool who were receiving bactrim (mean= 2.81, SD = 0.09 µg/ml for phenytoin; mean = 44.0, SD = 1.1 µg/ml for valproate). However, when normal serum pool was supplemented with 4.4 mg/dl of bactrim (concentration of bactrim in HIV pool) and supplemented with the same concentration of phenytoin or VPA, the observed free concentrations were much lower (mean = 1.65, SD = 0.05 µg/ml for phenytoin; mean = 26.1, SD = 1.4 µg/ml for valproate).			
DiCenzo R, Peterson D, Cruttenden K, Morse G, Riggs G, Gelbard H, Schifitto G (2004) Effects of valproic acid coadministration on plasma efavirenz and lopinavir concentrations in human immunodeficiency virus-infected adults. Antimicrob Agents Chemother.48:4328–4331.	Case series	In 11 HIV-positive subjects taking efavirenz 600 mg/day, authors found that efavirenz AUC was not significantly affected (mean change 0%, CI **)** 15% to 17%) after administration of VPA 500 mg/day for 7 days	None	Only PK analysis	POOR
Lertora JJ, Rege AB, Greenspan DL, Akula S, George WJ, Hyslop NE Jr,Agrawal KC (1994) Pharmacokinetic interaction between zidovudine and valproic acid in patients infected with human immunodeficiency virus. Clin Pharmacol Ther.56:272–278.	Open label, case series	In a class II open-label study, six patients with HIV received zidovudine 100 mg every 8 h, valproic acid 250 mg every 8 h was added on days 6–9. Zidovudine levels were measured on days 5 and 10. Co-administration with valproic acid resulted in mean zidovudine AUC increase from 0.65 to 1.17 mg/h/L ($p < 0.05$).	None	Only PK, sample size	POOR
DiCenzo R, Peterson D, Cruttenden K, Morse G, Riggs G, Gelbard H, Schifitto G (2004). Effects of valproic acid coadministration on plasma efavirenz and lopinavir concentrations in human immunodeficiency virus-infected adults. Antimicrob Agents Chemother.48:4328–4331.	11	When co-administered, VPA has demonstrated increased serum levels of the protease inhibitor lopinavir/ritonavir and the nucleoside reverse transcriptase inhibitor zidovudine.	None		POOR

[New 2015]

Table 6. Evidence of newer generation AEDs (including levetiracetam, lacosamide, gabapentin, pregabalin) interaction with ARVs

Antiepileptic medication	Reference	Design	Outcome	Indirectness	Other limitations	Quality
Levetiracetam	Locatelli P et al. (2004). Levetiracetam use in patients with HIV infection taking retroviral therapy [abstract]. European Journal of Neurology.4;11(Suppl 2):224.	No data available	-	-	-	-
Lacosamide	Van der Lee MJ et al. (2006). Lopinavir/ritonavir reduces lamotrigine plasma concentrations in healthy subjects. Clinical pharmacology and Therapeutics.80(2):159–168.	Case control	Lopinavir/ritonavir decreases the AUC of lamotrigine, probably by induction of glucuronidation. A dose increment to 200% of the initial lamotrigine dose is needed to achieve concentrations similar to those with lamotrigine alone. Lamotrigine does not appear to affect the pharmacokinetics of lopinavir/ritonavir.	None	No clinical variables, small sample size (24)	MODERATE
	van Luin M et al. (2009). The effect of raltegravir on the glucuronidation of lamotrigine. Journal of clinical pharmacology. 49(10):1220–1227	Open-label, randomized, 2-period, crossover, single-centre, phase I, multiple-dose trial	The mean ratio of the $AUC_{0 \rightarrow 48}$ of lamotrigine-2N-glucuronide to lamotrigine was similar when lamotrigine was taken alone (0.35) or when taken with raltegravir (0.36). Raltegravir does not influence the glucuronidation of lamotrigine	None	No clinical variables, small sample size (12)	POOR
Gabapentin	Hahn K et al. (2004). A placebo-controlled trial of gabapentin for painful HIV-associated sensory neuropathies. Journal of Neurology.251:1260-1266	Randomized control trial	Somnolence was the most frequently reported side effect in 80% of GBP treated patients in a range from mild to severe. This was significant ($p<0.05$) compared with the placebo-group. Dizziness, gait ataxia and nausea were also more frequent in the GBP-group, but compared with placebo-treated patients not statistically significant.	None	Small sample size (26), adverse events not correlated with ARV regimen	MODERATE
Pregabalin	Simpson DM et al. (2014). A randomized, double-blind, placebo-controlled trial and open-label extension study to evaluate the efficacy	Randomized control trial	68.9% of patients with any AEs in the pregabalin group, 60.9% in the placebo arm. Equal number of patients with serious adverse events. N=377	None	Did not evaluate ARV use	MODERATE

Antiepileptic medication	Reference	Design	Outcome	Indirectness	Other limitations	Quality
	and safety of pregabalin in the treatment of neuropathic pain associated with human immunodeficiency virus neuropathy. Pain.155(10):1943-54		(pregabalin, n=183; placebo, n=194)			

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Evidence to recommendation table

Benefits	Seizures are a cause of significant morbidity and mortality in HIV-positive patients and should be managed with AEDs that are safe and effective. In HIV-positive patients requiring AEDs and who are also on ARV medications, the optimal medication choice must be considered alongside the risk of drug-drug interactions and effects on HIV viral suppression. Liedtke et al. (2004) concluded that valproic acid and newer AEDs may provide useful alternatives to first-generation agents. Among the second-generation AEDs, levetiracetam, gabapentin and lamotrigine are not prone to altering metabolism of other medications through CYP450 enzyme induction and appear the most promising for patients on ARV therapy who require adjunctive therapy for partial seizures. Siddiqi and Birbeck (2013) reported that when newer AEDs are not available, valproic acid is a reasonable choice, as it will not cause a drug-drug interaction that can result in ARV failure.
Harms	There are concerns regarding drug-drug interactions when using certain combinations of ARV medications and AEDs. These interactions can result in reduction or increase in either antiepileptic or antiretroviral medications levels leading to loss of efficacy in either the AED (resulting in increased seizures) and/or antiretroviral medication (resulting in loss of viral suppression). These interactions

	can also lead to the development of resistance to ARV medications and/or adverse effects of ARV medications and/or AEDs. There are only a few PK studies addressing possible interactions between AEDs and ARVs; however, the available studies shows that co-administration of highly active ARV therapy containing a PI or NNRTI and an EI-AED possibly results in higher virologic failure rates. Phenytoin possibly reduces lopinavir and ritonavir, which may require a dosage increase of about 50%, and valproic acid could require a reduction of zidovudine (Birbeck et al., 2012) and, therefore, should be administered with caution and monitoring. Valproic acid is an enzyme-inhibiting agent and when co-administered, has demonstrated increased serum of levels of the protease inhibitor lopinavir/ritonavir and the nucleoside reverse transcriptase inhibitor zidovudine. Although newer AEDs seem not to interact with ARVs, there are not enough studies comparing both treatments and the therapeutic and toxic ranges are not well established for newer AEDs (Lietdke et al., 2004).
Summary of the quality of evidence	For the interaction between ARV medications and the older AEDs, the quality of evidence is poor or very poor. Most of the evidence comes from small case-series studies or case reports. These studies presented data mainly on the PK interaction without clinical outcomes. There are no RCTs. There are limited studies of the interaction between the newer AEDs and ARVs with moderate or low quality. There are no studies on the interaction between the AEDs and ARV medications in children.

Values and preferences	HIV and epilepsy comorbidity is common and presents a clinical challenge, given interactions between commonly available medications. As both conditions are highly stigmatized, a reduction in symptoms could lead to a significant improvement in quality of life.
Feasibility (including	Phenobarbital, phenytoin, carbamazepine and valproic acid are on the WHO Essential Medicine List.

resource use considerations)	Changes in the dose of either AEDs or ARVs could affect feasibility, considering that the overall cost of treatment could increase and that monitoring and implementation of different therapeutics strategies across the age spectrum could affect the workload for health workers. WHO ARV guidelines recommend the use of viral load monitoring for treatment response associated with the use of any ARVs. However, widely used viral load monitoring may not be feasible in all settings. It is particularly important to examine possible medication interactions for patients on poly-therapy. The newer AEDs are not on the WHO Essential Medicine List and so are more expensive. Facilities for routine AED monitoring are either not available or can be expensive in many countries.
Uncertainty or variability?	There is still uncertainty about the possible drug-drug interactions between different AEDs and ARVs. Viral load monitoring could be used as a minimum safety indicator to ensure that the use of AEDs is not decreasing the efficacy of ARVs. Clinical monitoring for symptoms or signs of AED toxicity should be carried out in all cases. Where AEDs blood monitoring is available and affordable, it should be implemented. There is major variability with regards to the availability and capacity for AED monitoring and viral load monitoring among countries and across different health settings.

[New 2015]

Recommendation and remarks

Recommendation

In comparison with enzyme-inducing anti-epileptic medications (phenobarbital, phenytoin, carbamazepine) or valproic acid, newer generation anti-epileptic medications that are not hepatically metabolized (i.e. leviteracetam, lacosamide, topiramate, gabapentin and pregabalin) may be preferred to use in people with HIV on certain antiretroviral medications (protease inhibitors or non-nucleoside reverse-transcriptase inhibitors).

If the treatment with newer generation anti-epileptic medications is not feasible, valproic acid is preferred over the enzyme-inducing anti-epileptic medications (phenobarbital, phenytoin, and carbamazepine). In all cases, close monitoring of HIV viral load and regular clinical monitoring is required. If resources are available, anti-epileptic medication levels should be monitored.

Rationale: HIV and epilepsy comorbidity is common and presents a clinical challenge, thus in HIV-positive patients requiring antiepileptic medications and who are also on antiretroviral medications, the optimal choice must be considered based on the risk of drug-drug interactions and effects on HIV viral suppression. Although the quality of the evidence is very low, newer antiepileptic medications and valproic acid may provide useful alternatives to first-generation agents. A feasibility issue is that the newer antiepileptic medications are not on the WHO Essential Medicine List and so are more expensive. In addition, facilities for routine antiepileptic drug level monitoring are either not available or can be expensive in many countries.

Remarks

Further research is needed in the following areas:

(1) Safety and efficacy of newer generation anti-epileptic medications (e.g., levetiracetam, lamotrigine, topiramate, pregabalin, and gabapentin) in patients on antiretroviral medications

(2) Clinical adverse effects in patients on antiretrovirals and anti-epileptic medications

(3) Further studies on the effects of hypoalbuminemia, hypergammaglobulenemia, and decreased gastrointestinal absorption on anti-epileptic medication levels in HIV-positive patients

(4) Interaction studies and safety and efficacy studies in children on anti-epileptic medications and antiretrovirals

Judgements about the strength of a recommendation

Factor	Decision
Quality of the evidence	□ High □ Moderate □ Low **X Very low**
Balance of benefits versus harms	□ Benefits clearly outweigh harms **X Benefits and harms are balanced** □ Potential harms clearly outweigh potential benefits
Values and preferences	**X No major variability** □ Major variability
Resource use	□ Less resource-intensive **X More resource-intensive**
Strength	**CONDITIONAL**

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[i] Area Under the Curve (AUC)
[ii] Enzyme-Inducing antiepileptic medication (EI-AED)
[iii] Highly active Antiretroviral therapy (HAART)
[iv] Non-enzyme-inducing antiepileptic medications (NEI-AEDs)
[v] Antiepileptic medication (AED)
[vi] Valproic acid (VPA)_
[vii] Nucleoside reverse transcriptase inhibitors (NRTIs)