

Management of Convulsions in HIV Positive Patients

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Abstract: *It is estimated that at least 10 percent of HIV patients experience seizures. HIV positive patients are prone for convulsions as part of neurological complications of the disease or they may be having associated epilepsy. It can also be a complication of metabolic abnormalities very commonly seen in HIV positive patients. It can be the presenting symptom in a HIV positive patient. Intracranial mass lesions and cerebral HIV infection seems to be the most likely cause of the seizures. The main concern in the management of convulsions in HIV positive patients is that there is lot of interaction between Anti Retroviral Treatment (ART) and anticonvulsants. The treating physician should know about these interactions so that suitable modification can be made in the anticonvulsant regimen and thereby prevent HIV viral resistance.*

Keywords: Anti Retroviral Treatment, Anticonvulsants, Drug Interaction, Viral Resistance

1. Introduction

Patients from HIV are prone for convulsions as part of neurological complications of the disease or they may be having associated epilepsy. A treating physician should know some of the basic aspects of managing convulsions in a HIV positive patient, since there are many drug-to-drug interactions between ART and anti-epileptics.

It is estimated that at least 10 percent of HIV patients experience seizures. It can occur at any stage. It can be the presenting symptom in a HIV positive patient. In majority of cases it is generalized seizures. It can also present as status epilepticus. Associated metabolic abnormalities may increase the risk for status epilepticus.¹ It can also present as simple and complex partial seizures. The frequent occurrence of generalized seizures and status epilepticus suggests that the HIV-infected brain has a low cortical excitability and impaired mechanisms for terminating seizure activity. Electro-encephalographic (EEG) findings are usually non-specific, diffuse slowing being the most common abnormality. Focal slowing and epileptiform activities are not commonly seen.¹

Aetiology

Intracranial mass lesions account for nearly half of the neurological disorders in AIDS patients.¹ Toxoplasmosis is the most common cause of intracranial mass lesions.¹ The diagnosis is usually made by demonstrating the presence of ring-enhancing lesions on CT scan, positive toxoplasma antibody titer, and clinical improvement with anti-toxoplasma treatment which is confirmed by repeat CT brain scan.¹ Primary CNS lymphoma is the second most common cause of AIDS-related intracranial mass lesions. It occurs in up to 2% of patients with AIDS.¹ Other mass lesions are Tuberculoma, Cryptococcal abscesses, Nocardial abscesses and Syphilitic gummas.¹

Other focal lesions without significant mass effect, such as progressive multifocal leukoencephalopathy (PML) may also be responsible for new-onset seizures in several AIDS patients.¹ In patients without mass lesions, meningo-encephalitis caused by some opportunistic infections is a frequent source of seizures. The incidence of meningitis and encephalitis in HIV-infected patients with new onset seizures varies from 12% to 16%. Cryptococcal meningitis is the most frequent meningoencephalitis producing seizures. To confirm the diagnosis, an India Ink preparation of CSF should be examined. If negative, cryptococcal antigen and fungal culture may increase the diagnostic yield.¹ Other causes which are likely to produce seizures in AIDS patients include tubercular meningitis and cerebrovascular diseases when accompanied by edema.

Infrequent causes include aseptic meningitis, Neurosyphilis, Herpes zoster, Leukoencephalitis, Toxoplasma and Cytomegalovirus encephalitis.¹ Approximately half of HIV-infected patients with seizures have no definite identifiable disease of the brain and cerebral HIV infection seems to be the most likely cause of the seizures.¹ HIV-related seizures may also be provoked by concurrently administered drugs for example foscarnet therapy,^{1,2} new-onset generalised seizures following a single topical application of lindane for scabies.² Seizures have occurred following antitubercular medication, especially when started on high-dose Isoniazid in HIV positive patients.²

We reviewed the literature to see whether there are any interaction between the anti-epileptics and the ART. We have discussed the interaction with each of the commonly used anti-epileptics.

Phenobarbitone

Coadministration of Phenobarbitone with Zidovudine has not been studied but Phenobarbitone may decrease Zidovudine concentrations as phenobarbital has been shown to induce

Zidovudineglucuronidation by 4-fold in rats. So monitoring of the response to HIV therapy has to be done.⁴

Coadministration of Phenobarbitone with Nevirapine has not been studied, but it may decrease Nevirapine concentrations.⁴ Specific interaction studies between Phenobarbitone and Efavirenz has not been studied. Coadministration may decrease phenobarbital and/or Efavirenz concentrations.^{4,5,6,7} Phenobarbitone may decrease Efavirenz levels by inducing CYP450 3A4.⁶ Coadministration of Phenobarbitone and Atazanavir has not been studied. Phenobarbital induces CYP3A4 and Atazanavir may be less effective due to decreased Atazanavir plasma concentrations.^{4,7} Phenobarbital will decrease the level and effect of Ritonavir by P-glycoprotein (MDR1) efflux transporter.

Phenobarbital, a potential enzyme inducer may via its action on UDP-glucuronyl transferases (UDT) slightly decrease the plasma concentrations of abacavir.⁴ The interaction between Lopinavir and Phenobarbitone has not been studied. Concentrations of Lopinavir may be decreased due to CYP3A4 induction by phenobarbital.^{4,6,8} Caution should be exercised in administering phenobarbital with Lopinavir/Ritonavir.

Co-administration of Darunavir/ Ritonavir with Phenobarbitone has not been studied.⁶ Darunavir/ Ritonavir may cause a decrease the concentrations of phenobarbital.⁴ Phenobarbitone may decrease Darunavir levels by inducing CYP450 and their co administration is contraindicated.^{4,6,8}

Concurrent use of Phenobarbital and Ritonavir may result in decreased phenobarbital plasma concentrations and loss of phenobarbital efficacy.⁷

Phenobarbital will decrease the level and effect of Maraviroc by P-glycoprotein (MDR1) efflux transporter.⁷ The recommended dose of Maraviroc when coadministered with phenobarbital is 600 mg twice daily (higher than the routine dosage). Coadministration is not recommended in patients with creatinine clearance <30 ml/min or on haemodialysis.⁴

Phenobarbital decreases levels of Elvitegravir/Cobicistat by affecting hepatic/intestinal enzyme CYP3A4 metabolism and hence its co administration is contraindicated as this may lead to loss of virologic response and possible resistance.^{4,6}

Rilpivirine should not be co-administered with phenobarbital as significant decreases in Rilpivirine plasma concentrations may occur due to CYP3A enzyme induction, which may result in loss of virologic response and possible resistance to Rilpivirine and other drugs in the class of NNRTIs.^{4,7}

Etravirine should not be used in combination with phenobarbital as co-administration may cause significant decreases in Etravirine plasma concentrations and loss of therapeutic effect of Etravirine.⁴ Phenobarbital will decrease the level and effect of Etravirine by affecting hepatic enzyme CYP2C19 metabolism.⁷

There is no Stavudine significant interaction with Stavudine(d4T), Lamivudine(3TC), Emtricitabine(FTC) and Tenofovir (TNF).⁴

Eptoin

Phenytoin blood levels have been reported to be low in some patients receiving Zidovudine, while in one patient a high level was noted.⁴ Zidovudine clearance is also decreased by 30% thus leading to increased Zidovudine concentration when both the drugs are used together.^{4,6,9}

Coadministration of Eptoin and Nevirapine is not studied, but Eptoin may decrease Nevirapine concentrations.⁴ Phenytoin will decrease the level and effect of Nevirapine by affecting hepatic/intestinal enzyme CYP3A4 metabolism.⁷

Phenytoin significantly reduces the levels of Efavirenz by inducing CYP3A4 and cases of antiretroviral treatment failure have been reported.⁴ Phenytoin is expected to reduce Efavirenz level through stimulation of cytochrome P450 (CYP) 3A4 and CYP2B6. Conversely, Efavirenz has been shown in vitro to inhibit the enzymes responsible for phenytoin metabolism, CYP2C9 and CYP2C19.^{6,7,10}

Coadministration of Phenytoin with Atazanavir has not been studied. Phenytoin induces CYP3A4 and Atazanavir may be less effective due to decreased Atazanavir plasma concentrations.^{4,7} Phenytoin will decrease the level and effect of Ritonavir by P-glycoprotein (MDR1) efflux transporter.⁷ Concurrent use of Phenytoin and Ritonavir may result in decreased Phenytoin (the active metabolite of fosphenytoin) plasma concentrations and/or decreased Ritonavir plasma concentrations.¹¹

Coadministration with Lopinavir decreases phenytoin concentrations and may decrease Lopinavir concentrations. Coadministration of Lopinavir/Ritonavir and Phenytoin results in two-way drug interaction through cytochrome P-450 induction.⁴ Phenytoin is an inducer of CYP450 isoenzyme CYP3A4 and would be expected to increase the metabolism of protease inhibitors. Phenytoin is principally metabolized by CYP2C9 and CYP2C19 and would therefore, not be expected to be substantially affected by most protease inhibitors.¹²

Potentially may slightly decrease Abacavir concentrations by affecting glucuronyl transferases.¹³ Phenytoin may decrease Darunavir levels by inducing CYP450 metabolism.^{6,12} The European SPC contraindicates coadministration as it may significantly decrease Darunavir concentrations. However, the US Prescribing Information predicts no change in Darunavir concentrations, but decreased Phenytoin concentrations and advises monitoring of Phenytoin.⁴

The recommended dose of Maraviroc when coadministered with phenytoin without a potent CYP3A inhibitor is 600 mg twice daily. Coadministration is not recommended in patients with creatinine clearance <30 ml/min or on haemodialysis.⁴

Concurrent use of Elvitegravir and Phenytoin may result in decreased plasma concentration of Phenytoin and/or Elvitegravir with reduced efficacy and possible viral resistance.¹¹

Coadministration of Phenytoin and Elvitegravir and Cobicistat has not been studied. Phenytoin induces CYP3A4 and could significantly decrease Elvitegravir and Cobicistat concentrations, which may result in loss of therapeutic effect and development of resistance.⁴

Coadministration of Phenytoin with Rilpivirine has not been studied. A significant decrease in Rilpivirine plasma concentrations is expected due to induction of CYP3A enzymes. This may result in loss of therapeutic effect of Rilpivirine and possible resistance to Rilpivirine and to other drugs in the NNRTI class.^{4,11}

Etravirine should not be used in combination with phenytoin as it is expected to decrease Etravirine concentrations. Phenytoin will decrease the level and effect of Etravirine by affecting hepatic/intestinal enzyme CYP3A4 metabolism. This may result in loss of therapeutic effect of Etravirine. In addition, Etravirine may inhibit the CYP450 metabolism of phenytoin, resulting in increased phenytoin concentrations.⁷ D4T, 3TC, FTC and TNF do not have significant interaction with Phenytoin.⁴ There is no information regarding interaction with Raltegravir.

Carbamazepine

Coadministration of Carbamazepine with Zidovudine has not been studied but Zidovudine may increase Carbamazepine concentrations due to competition for glucuronidation (carbamazepine is glucuronidated by UGT2B7).⁴

Coadministration of Nevirapine with Carbamazepine may decrease Carbamazepine concentrations. Dose adjustment may be needed due to possible decrease in clinical effect.⁴ Concurrent use of Carbamazepine and Nevirapine may result in reduced Nevirapine plasma concentrations and risk of diminished therapeutic effect of Nevirapine, including loss of virologic response and development of resistance. Concurrent use is contraindicated.¹¹ Nevirapine will decrease the level and effect of Carbamazepine by affecting hepatic/intestinal enzyme CYP3A4 metabolism.⁷

Co-administration of Efavirenz (600 mg once daily) with Carbamazepine (400 mg once daily) decreased carbamazepine AUC, C_{max} and C_{min} by 27%, 20% and 35%, respectively, while Efavirenz AUC, C_{max} and C_{min} decreased by 36%, 21%, and 47%, respectively.^{4,14} Carbamazepine which is a potent inducer of CYP3A4 increases the metabolism of Efavirenz which is primarily metabolized by CYP450 isoenzyme CYP3A4. Efavirenz is also an inducer of CYP3A4 and so it can increase the metabolism of CBZ. From the study and case reports, concurrent use of CBZ and EFV reduce the levels of both the drugs and this may also lead to treatment failure.^{7,8,5,11}

Coadministration of Carbamazepine with Atazanavir has not been studied but could potentially increase carbamazepine concentrations and reduce Atazanavir concentrations (especially without Ritonavir).⁴ Ritonavir is a potent inhibitor of CYP3A4 and markedly increases Carbamazepine levels

and toxicity. Moreover, Carbamazepine is an inducer of CYP3A4 and therefore can increase the metabolism of protease inhibitors causing the levels to become subtherapeutic.⁸ Carbamazepine will decrease the level or effect of Ritonavir by affecting hepatic/intestinal enzyme CYP3A4 metabolism.⁷

Coadministration of Carbamazepine with Lopinavir may result in a marked decrease in concentrations of Lopinavir and increased concentrations of Carbamazepine.^{4,7}

Coadministration of Abacavir with Carbamazepine has not been studied but Abacavir may increase Carbamazepine concentrations due to competition for glucuronidation (Carbamazepine is glucuronidated by UGT2B7). The clinical relevance of this interaction is unknown as the importance of glucuronidation in the overall metabolic process of Carbamazepine is controversial.⁴

Coadministration of Carbamazepine with Darunavir had no significant effect on Darunavir exposure, but Carbamazepine's AUC, C_{max} and C_{min} are increased by 45%, 43% and 54% respectively. No dose modification of Darunavir/Ritonavir or Carbamazepine is required when initiating therapy. Carbamazepine concentrations should be monitored and dose titration is recommended. Based on the findings, the Carbamazepine dose may be reduced by 25% to 50%.^{4,6} While a few literatures state that Carbamazepine show no significant change in Darunavir levels, others state that Carbamazepine may decrease Darunavir levels by inducing CYP450 wherein the combination should be avoided and alternate agents be considered.^{6,7,14}

Coadministration of Carbamazepine with Ritonavir may increase the plasma concentrations of Carbamazepine due to inhibition of CYP3A4 by Ritonavir. Coadministrations should be used with caution. Careful monitoring of adverse effects and therapeutic concentrations of CBZ is recommended. Two case reports of increased Carbamazepine concentrations in patients receiving Ritonavir (400mg twice daily) have been reported.⁴

The recommended dose of Maraviroc when coadministered with carbamazepine is 600 mg twice daily. Coadministration is not recommended in patients with creatinine clearance < 30 ml/min or on haemodialysis.⁴ Carbamazepine will decrease the level and effect of Maraviroc by affecting hepatic/intestinal enzyme CYP3A4 metabolism.⁷

Coadministration of Raltegravir and Carbamazepine has not been studied but Carbamazepine could potentially decrease Raltegravir concentrations as it is mainly glucuronidated by UGT1A1 and in vitro data suggest that Carbamazepine induces UGT1A1.⁴

Carbamazepines potentially decrease Elvitegravir/Cobicistat effects. Carbamazepine decreases levels of Elvitegravir by affecting hepatic/intestinal enzyme CYP3A4 metabolism. This may lead to loss of virologic response and possible resistance.^{4,7}

Significant decreases in Rilpivirine plasma concentrations are expected due to induction of CYP3A enzymes when used in combination with Carbamazepine. This may result in

loss of therapeutic effect of Rilpivirine and possible resistance to Rilpivirine and other drugs in the NNRTI class.^{4,7}

Etravirine should not be used in combination with Carbamazepine as co-administration may cause significant decreases in Etravirine plasma concentrations and loss of therapeutic effect of Etravirine.⁴ Carbamazepine will decrease the level or effect of Etravirine by affecting hepatic enzyme CYP2C9/10 metabolism.⁷

Oxcarbazepine

Coadministration of Oxcarbazepine with Nevirapine has not been studied but could potentially decrease Nevirapine exposure, although to a moderate extent, as Oxcarbazepine is a moderate inducer of CYP3A4. No a prior dose adjustment is recommended, but HIV infection (e.g. viral load, CD4 count) should be monitored.⁴

Oxcarbazepine will decrease the level and effect of Efavirenz by affecting hepatic/intestinal enzyme CYP3A4 metabolism.^{4,7}

Oxcarbazepine is a moderate inducer of CYP3A4 and could potentially decrease Atazanavir or Atazanavir/Ritonavir exposure although to a moderate extent.^{4,7}

Coadministration of Oxcarbazepine with Lopinavir/Ritonavir has not been studied. Oxcarbazepine is a moderate inducer of CYP3A4 and could potentially decrease Lopinavir/Ritonavir exposure although to a moderate extent.⁴ Coadministration of Oxcarbazepine with Darunavir has not been studied. Oxcarbazepine is a moderate inducer of CYP3A4 and could potentially decrease Darunavir/Ritonavir exposure although to a moderate extent.^{4,7}

Coadministration of this drug with Maraviroc has not been studied but could potentially decrease Maraviroc concentrations. Maraviroc is metabolized by CYP3A4 and Oxcarbazepine induces CYP3A4, but to a lesser extent than Carbamazepine.^{4,7}

Oxcarbazepine decreases levels of Elvitegravir and Cobicistat by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Coadministration of these drugs is contraindicated. This may lead to loss of virologic response and possible resistance.^{4,6}

Coadministration of Oxcarbazepine with Rilpivirine is contraindicated as it significantly decreases the Rilpivirine plasma levels by affecting hepatic/intestinal enzyme CYP3A4 metabolism. There is a Potential for loss of virologic response and possible resistance to Rilpivirine and the NNRTI class.^{4,7}

Coadministration of Oxcarbazepine and Etravirine has not been studied but could potentially decrease Etravirine exposure, although to a moderate extent, as Oxcarbazepine is a moderate inducer of CYP3A4. No prior dose adjustment is recommended, but HIV infection (e.g. viral load, CD4 count) should be monitored.⁴ Oxcarbazepine may increase or decrease the effect of Etravirine by affecting Hepatic

enzyme CYP2C19 or CYP3A4 metabolism respectively.⁷ There is no interaction of Oxcarbazepine with AZT, d4T, 3TC, FTC, TNF, ABC and Raltegravir.⁴

Sodium Valproate

Zidovudine AUC levels increased by ~80% with valproate. Valproic acid increases the levels of Zidovudine by decreasing its metabolism. Routine dose modification of Zidovudine is not warranted with coadministration, but patients should be monitored closely for potential toxicity of Zidovudine. Severe anemia and liver toxicity has been reported.^{11,13}

Coadministration of Sodium Valproate with Atazanavir has not been studied. Atazanavir alone is unlikely to alter valproate concentrations. Atazanavir/Ritonavir may decrease the plasma concentration of valproate by induction of glucuronidation by Ritonavir. Careful monitoring of Valproate concentrations and/or therapeutic effect is recommended.⁴

Sodium Valproate increased Lopinavir effects by possible inhibition of UGT-mediated metabolism of Lopinavir.⁶ Coadministration of this drug with Darunavir has not been studied. Darunavir/Ritonavir may decrease the plasma concentration of Valproate by induction of glucuronidation by Ritonavir.^{4,11} Coadministration with Elvitegravir has not been studied. Valproate is mainly metabolized by CYP2C9 and CYP2C19. Elvitegravir is a modest inducer of CYP2C9 and therefore could potentially decrease valproate concentrations.⁴

But Sodium valproate can be safely used with most of the other ART drugs like d4T, 3TC, FTC, NVP, TNF, EFV, ABC, Maraviroc, Raltegravir, Rilpivirine, Etravirine and not much information is known with Cobicistat.^{4,7} But the biggest drawback of Sodium valproate is that it has been found to stimulate the replication of HIV type-1.¹⁵ Though it can be combined with most of the first line regimen ART, it is better to avoid this drug due to the above mentioned cause.

Levetiracetam

Levetiracetam is one of the safest drugs that can be used with most of the ARTs. It can be safely used with AZT, d4T, 3TC, FTC, TNF, ABC, NVP, EFV, LPV/Rtv, ATV/Rtv, DRV/Rtv, Raltegravir, Elvitegravir, Rilpivirine, Etravirine and Maraviroc.⁴ Coadministration of Levetiracetam with Cobicistat has not been studied, but based on metabolism and clearance a clinically relevant drug interaction is unlikely. Levetiracetam undergoes enzymatic hydrolysis (non CYP) and is eliminated unchanged in the urine by glomerular filtration.⁴

Gabapentin

Coadministration of Gabapentin with most of the ART medicines is not studied. But based on metabolism and clearance, a clinically relevant drug interaction is unlikely as Gabapentin is cleared mainly by glomerular filtration. Therefore there is no interaction of Gabapentin with the

following ART drugs like AZT, d4T, 3TC, FTC, TNF, NVP, EFV, ATV/Rtv, LPV/Rtv, ABC, DRV/Rtv, Maraviroc, Raltegravir, Elvitegravir, Cobicistat, Rilpivirine and Etravirine.⁴

Pregabalin

Similar to Gabapentin, coadministration of Pregabalin with most of the ART medicines is not studied. But based on metabolism and clearance, a clinically relevant drug interaction is unlikely as Pregabalin is cleared mainly by glomerular filtration. Therefore there is no interaction of Pregabalin with the following ART drugs like AZT, 3TC, FTC, NVP, EFV, TNF, ATV/Rtv, LPV/Rtv, ABC, DRV/Rtv, Maraviroc, Raltegravir, Elvitegravir, Cobicistat, Rilpivirine and Etravirine.⁴

Topiramate

Though the coadministration of Topiramate with the FDA approved ART drugs has not been studied, based on the metabolism and clearance, a clinically significant interaction is unlikely. However, when coadministered with Tenofovir, periodic monitoring of renal function is recommended as both the drugs can cause renal problems (Nephrolithiasis with Topiramate and Fanconi's syndrome with Tenofovir).⁴ Similarly Tiagabine is said to be having less interaction with the ARTs and can safely be used with ARTs.¹⁶

Zonisamide and Tiagabine

Not much information is available with these 2 drugs regarding interaction with the ART drugs. Coadministration of Tiagabine with Efavirenz may decrease the plasma concentrations of Tiagabine due to induction of CYP3A4 by Efavirenz. Caution to be used if both the drugs are used concomitantly.¹⁷ However, Tiagabine can be used as an alternative agent with anti-retroviral agents when other antiepileptics are to be possibly avoided.⁶ Some of the drugs like Diazepam and Lorazepam are used in acute management of convulsions and also in Status Epilepticus. We searched the literature to see whether there was any interaction between those drugs and the ART.

Diazepam

There is no interaction between diazepam and the following ART drugs like AZT, d4T, 3TC, FTC, TNF, ABC, Maraviroc, Raltegravir, Cobicistat and Rilpivirine.⁴ Nevirapine and Efavirenz will decrease the level and effect of Diazepam by affecting hepatic/intestinal enzyme CYP3A4 metabolism.^{4,7} Atazanavir and Ritonavir increases levels of Diazepam by affecting hepatic/intestinal enzyme CYP3A4 metabolism. There will be increased toxicity. Lowering of Diazepam has to be considered.⁷

Similarly Lopinavir/Ritonavir and Darunavir/ Ritonavir could potentially increase Diazepam exposure by inhibition of CYP3A4 and 2C19. This could prolong sedation and a dosage reduction may be required.^{4,7,11} Coadministration of Diazepam with Elvitegravir/Cobicistat has not been studied. Diazepam is metabolized to Nordiazepam (by CYP3A4 and 2C19) and to Temazepam (mainly by CYP3A4). Elvitegravir/Cobicistat could potentially increase Diazepam exposure by inhibition of CYP3A4. This could prolong sedation and a dosage reduction may be required.⁴ Coadministration may increase plasma concentrations of Diazepam. A decrease in diazepam dose may be needed.⁴

Lorazepam

Lorazepam possibly causes a modest increase in the bioavailability of Zidovudine and concurrent use can increase the incidence of headaches.¹⁸ Coadministration of Lorazepam with Elvitegravir/Cobicistat has not been studied, but based on the metabolism and clearance a clinically significant drug-drug interaction is unlikely. Lorazepam is mainly glucuronidated and there is no evidence that Elvitegravir/Cobicistat inhibits or induces UDP-glucuronosyltransferase (UGTs).⁴ There is no interaction of Lorazepam with d4T, 3TC, FTC, TNF, NVP, EFV, ATV/Rtv, LPV/Atv, ABC, DRV/Rtv, Maraviroc, Raltegravir, Rilpivirine and Etravirine.⁴

Comparison

The antiepileptics which can be combined with ART and those which have to be avoided are summarized in the table below.

Anti Epileptics	Anti Retroviral Drugs		
	Can be used	Cannot be used	No Information
Phenobarbitone	d4T, 3TC, FTC, TNF	AZT, NVP, EFV, ATV/Rtv, LPV/Rtv, ABC, DRV/Rtv, Maraviroc (dose has to be increased)	Raltegravir, Elvitegravir, Cobicistat, Rilpivirine, Etravirine
Eptoin	d4T, 3TC, FTC, TNF	AZT, NVP, EFV, LPV/Rtv, ABC, DRV/Rtv, Elvitegravir, Etravirine, ATV/Rtv, Cobicistat, Maraviroc (Coadministration not recommended if GFR < 30ml/min and Hemodialysis)	Raltegravir, Rilpivirine
Carbamazepine	d4T, 3TC, FTC, TNF	AZT, NVP, EFV, DRV/Rtv, Maraviroc (dose has to be increased), Raltegravir, Elvitegravir, Cobicistat, Rilpivirine, Etravirine	ATV/Rtv, LPV/Rtv, ABC
Oxcarbazepine	AZT, d4T, 3TC, FTC, TNF, ABC, Raltegravir	NVP, EFV, Maraviroc, Eltegravir, Cobicistat, Rilpivirine	ATV/Rtv, LPV/Rtv, DRV/Rtv, Etravirine
Sodium Valproate	d4T, 3TC, FTC, TNF, NVP, EFV, ATV, ABC (not studied), Maraviroc, Raltegravir,	AZT, RTV, LPV, DRV, Eltegravir	Cobicistat

	Rilpivirine, Etravirine		
Levetiracetam	AZT, d4T, 3TC, FTC, NVP, EFV, TNF, ABC, Raltegravir, ATV/Rtv, LPV/Rtv, DRV/Rtv, Maraviroc, Eltegravir, Cobicistat (not studied), Rilpivirine, Etravirine		
Diazepam	AZT, 3TC, FTC, d4T, TNF, ABC, Maraviroc, Raltegravir, Rilpivirine,	NVP and EFV decrease the level of Diazepam. ATV, LPV/Rtv, DRV/Rtv, Eltegravir, Cobicistat and Etravirine increase the level of Diazepam - hence decrease the dose of Diazepam.	
Lorazepam	d4T, 3TC, FTC, TNF, NVP, EFV, ATV/Rtv, LPV/Rtv, ABC, DRV/Rtv, Maraviroc, Raltegravir, Elvitegravir, Cobicistat(not studied), Rilpivirine, Etravirine	Increases the level of Zidovidine and can cause headache	
Gabapentin	3TC, FTC, TNF, EFV, Cobicistat(not studied), AZT, d4T, NVP, ATV/Rtv, LPV/Rtv, ABC, DRV/Rtv, Maraviroc, Raltegravir, Eltegravir, Rilpivirine, Etravirine		
Pregabalin	3TC, FTC, TNF, AZT, d4T, NVP, EFV, ATV/Rtv, LPV/Rtv, ABC, DRV/Rtv, Maraviroc, Raltegravir, Elvitegravir, Rilpivirine, Etravirine		Cobicistat
Topiramate	AZT, d4T, 3TC, FTC, TNF, NVP, EFV, ATV/Rtv, LPV/Rtv, ABC, DRV/Rtv, Maraviroc, Raltegravir, Cobicistat, Rilpivirine, Etravirine		Elvitegravir
Tiagabine	AZT, d4T, 3TC, FTC, TNF, NVP, EFV, ATV/Rtv, LPV/Rtv, ABC, DRV/Rtv, Maraviroc, Raltegravir, Cobicistat, Rilpivirine, Etravirine		Elvitegravir
Not much Information regarding Zonisamide is available			

2. Management of Convulsions in a HIV positive patient

Since drug level monitoring is not routinely done in most of the health setup, the Department of Medicine, JSS Medical College, Mysore, South India came up with a protocol to manage convulsions in HIV positive patients after going through the literature regarding ART and anticonvulsants.

3. When the patients comes to the Emergency Department

If the patient with known HIV positive patients comes to the emergency room and if the details of the ART are not known, Levetiracetam is the drug of choice in the acute management of convulsions. If the patient is not on any ART, than it can be managed just like any other case. Drugs like Phenytoin, Diazepam, Lorazepam, Phenobarbitone and Levetiracetam can be used parenterally. Sodium Valproate could have been used, but as mentioned before it may increase the load of HIV type-1.

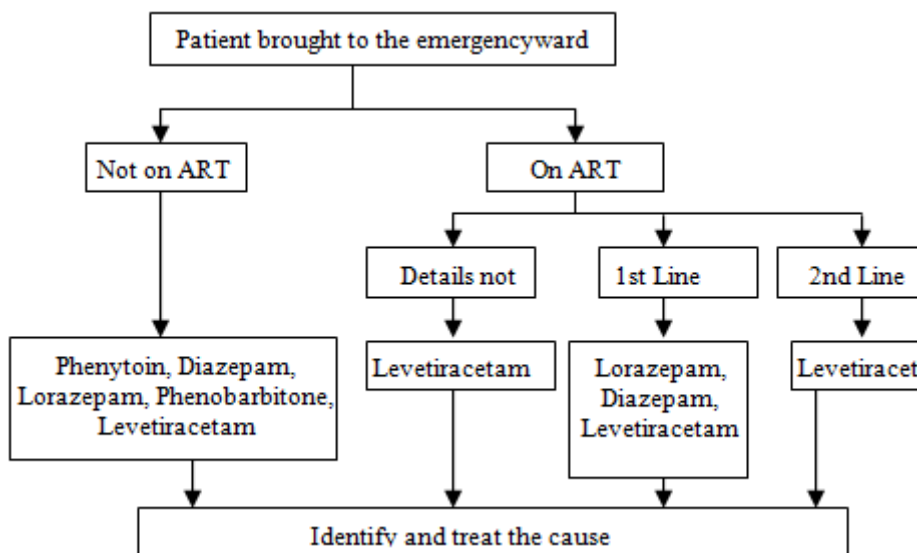
If the patient is on ART and the details of the treatment are not available, then the drug of choice is Levetiracetam. But if the patient is on first line regimen with either of the drugs like AZT, 3TC, FTC, TNF, ABC, NVP and EFV, Lorazepam can also be tried for the management of acute episodes. But Lorazepam can increase the bioavailability of AZT and can cause headache. If Diazepam is to be used,

than the dose of Diazepam may have to be increased as NVP and EFV decreases the level of Diazepam.

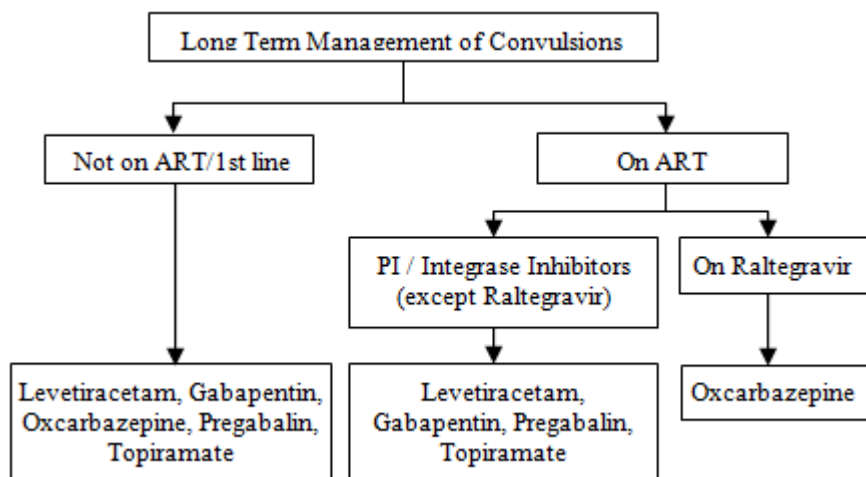
If the patient is on Protease Inhibitor based regimen like Atazanavir, Ritonavir, Darunavir and Lopinavir, or on Integrase inhibitor like Raltegravir, Eltegravir/Cobicistat, CCR5 inhibitor, Maraviroc or newer NNRTIs than the drug that can be used is only Levetiracetam. In the meantime, the primary cause for convulsions has to be identified and managed accordingly.

4. Long term management of Epilepsy

When the patient has to put on long term anticonvulsants, even if the patients are not on ART, the patients should be started on anticonvulsants which do not have interaction with first line ART regimen (drugs like AZT, 3TC, FTC, NVP, TDF, EFV and ABC). Drugs like Levetiracetam, Oxcarbazepine, Gabapentin, Pregabalin and Topiramate can be used. But the patients should be counseled that they should inform about their treatment details to the HIV physician who is going to start ART. If the patient is on Protease Inhibitors, Integrase Inhibitors (except Raltegravir) or CCR5 Inhibitors than the patient can be started on Levetiracetam, Gabapentin, Pregabalin and Topiramate. Oxcarbazepine can be used, if the patient is on Raltegravir. The details of the management of epilepsy in a HIV positive patient are depicted in the flow chart given below.



Flow Chart 1: Management of Convulsions in a HIV positive patient in the Emergency Ward



Flow Chart 2: Long Term Management of Convulsions in HIV Positive patients

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