SUGGESTIONS FOR MANAGEMENT OF ANTICONVULSANT-ANTIRETROVIRAL INTERACTIONS IN HIV

Avoid: **carbamazepine, phenytoin, phenobarbital, primidone, felbamate, oxcarbazepine when possible**

- **All are enzyme inducers and can decrease protease inhibitor, NNRTI and elvitegravir/cobicistat levels, which may impact viral efficacy. If these anticonvulsants are required, consult interaction table for suggested dosage adjustments or alternatives.**
- In the U.S. Military HIV Natural History Study, virologic response was assessed in 19 patients taking enzyme-inducing (EI) antiepileptics (AEDs) (n=12 phenytoin, n=6 carbamazepine, n=1 phenobarbital) versus 85 patients taking non-enzyme inducing antiepileptics (n=88 gabapentin, n=2 pregabalin, n=1 levetiracetam) while on cART concomitantly for at least 28 consecutive days. Virologic failure was defined as having 2 consecutive viral loads ≥400 copies/mL after 6 months of cART or having all VLs in the first 6 months of cART ≥400 c/mL. Patients on EI-antiepileptics had significantly greater virologic failure (10/16, 63%) compared to other AED patients (20/75, 27%) for the first cART/AED period (OR 4.6 [1.5-14.3];P<0.01). Average VL was also greater during cART in the EI-AED group (3.3 log +/-1.3) than the other AED group (2.4 log +/-1.2; P<0.01). A multivariate model adjusting for both year starting and VL at cART showed similar results (OR 4.7 [0.9-23.6]; P=0.06). Analysis of multiple overlap periods yielded consistent and significant results with higher rates of VF in the EI-AED group (OR 4.2 [1.5-11.4]; P<0.01). Therefore, concurrent use of enzyme-inducing anti-epileptics and cART should be avoided whenever possible.[Okulicz et al. 2011]

1) Depending on seizure type, ***consider using other 2nd-line anticonvulsants*** to minimize interactions with protease inhibitors, NNRTIs and elvitegravir/cobicistat.

Best choices:

- Gabapentin (Neurontin®)
- Lamotrigine (Lamictal®): a significant decrease in lamotrigine concentrations may be seen when used with ritonavir-based regimens
- Levetiracetam (Keppra®)
- Vigabatrin (Sabril®)
- Pregabalin (Lyrica®)

Caution Warranted:

- Valproic acid (Epival®, Depakene®): monitor viral load closely; avoid combination with zidovudine due to cases of severe anemia
- Zonisamide (Zonegran®, USA): potential for increased zonisamide concentrations; a decreased dose may be required
- Topiramate (Topamax®): small potential for increased topiramate concentrations; topiramate is a mild CYP3A4 inducer (may impact PI, NNRTI and elvitegravir/cobicistat concentrations)
- Tiagabine (Gabitril®, USA): potential for increased tiagabine concentrations; a decreased dose may be required
- Anticonvulsants and protease inhibitors and/or tenofovir- potential for additive bone toxicity (osteonecrosis, osteopenia)

2) ***Change antiviral or drug dose if possible***:

- If possible, consider using a raltegravir-based regimen.

- Use ritonavir boosted protease inhibitor regimens (minimum ritonavir) 200mg/day to overcome induction. This is still a preliminary recommendation, since data are limited with this approach. Therapeutic drug monitoring of antiretrovirals is recommended if available.
- Empirically increase Kaletra (lopinavir/ritonavir) dose to 3 tablets BID (i.e. 600/150 mg BID) when combined with enzyme inducing

anticonvulsants. This is still a preliminary recommendation, since data are limited with this approach. Therapeutic drug monitoring of both the antiretrovirals and anticonvulsants is recommended if available (see table for details).

- Preliminary evidence suggest that darunavir/ritonavir (DRV/RTV) combined with carbamazepine may be a viable option. Although it is unlikely the dose of DRV/RTV requires adjustments, a 25-50% decrease in carbamazepine dose may be required. Therapeutic drug monitoring of both the antiretrovirals and carbamazepine is recommended if available (see table for details).

Appendix I: Antiepileptic Drugs of Choice in the General Population

Seizure Type	First-line Therapy	Second-line Therapy
a) Generalized		
Tonic-Clonic	VPA, CBZ, PHT	CLB, FBM, ?GBP, LTG, ?LEV, OXC, PB, PRM, ?TGB, TPM, ?VGB, ZNS
Absence	VPA, ESM	AZM, CLB, ?FBM, LTG, ?LEV, ?TPM, ZNS
Myoclonic	VPA	AZM, CLB, CZP, ?FBM, ?LTG, ?LEV, ?TPM, ZNS
Atonic	VPA	CLB, FBM, LTG, TGM
b) Partial		
Simple or complex ± secondary generalization	CBZ, PHT	CLB, FBM, GBP, LTG, LEV, OXC, PB, PGB, PRM, TGB, TPM, VGB, VPA, ZNS
Benign rolandic epilepsy	CBZ	CLB, GBP, PHT
Juvenile myoclonic epilepsy	VPA	CLB, LTG, TPM, CBZ, PHT (for gen. T-C seizures)
Lennox-Gastaut	VPA	CLB, CZP, FBM, LTG, TPM, VGB
West Syndrome (infantile spasms)	VGB superior toACTH	CLB, CZP, LTG, steroids, VPA
c) Women		
Idiopathic generalized epilepsy	VPA	
Idiopathic generalized epilepsy (pregnancy)	LTG	

ACTH= adrenocorticotropic hormone; AZM= acetazolamide; CBZ= carbamazepine; CLB= clobazam; CZP= clonazepam; ESM= ethosuximide; FBM= felbamate; GBP= gabapentin; LTG= lamotrigine; LEV= levetiracetam; OXC= oxcarbazepine; PB= phenobarbital; PGB= pregabalin; PHT= pheytoin; PRM= primidone; TGB= tiagabine; TPM= topiramate; VGB= vigabatrin; VPA= valproic acid; ZNS= zonisamide. ? = unclear

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