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Potential Benefits for the Brain Using Kick&Kill Strategies: The Other Side of the Coin?

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Background (I)

1) The use of new agents for HIV cure should cover safety at different settings including the central nervous system (CNS).

2) Reactivating latent HIV could increase CNS infection potentially inducing neurological affectation.

3) Antiretroviral therapy interruption appears to be a requirement as a proof of cure, which could be harmful due to additional neuroinflammation or neurotoxicity.

Background (II)

1) Purge of HIV reservoir should imply lower presence of latent HIV, which may positively affect the CNS reservoir.

2) Neurocognitive benefits have been also shown after antiretroviral pause, hypothetically by preventing antiretroviral-related neurotoxicity.

3) Some agents proposed for HIV cure may exert advantageous properties for CNS, such as class I histone deacetylase inhibitors (HDACIs), which have shown beneficial effects on neurocognition.

Methods

- ***Public Databases***:

We searched Pubmed, Clinicaltrials.gov, and Eudract databases: ***until March 2018***.

- ***Setting***:

Human clinical studies testing HDACIs in the setting of HIV cure and *kick&kill* strategies.

- ***Targeted Projects***:

1) Past research: published reports.

2) Ongoing trials: stated in public official databases.

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Results (I)

- ✓ We found 280 studies investigating HDACIs as potential HIV eradication strategies, **22 in humans**.

- ✓ Drugs most frequently tested were:

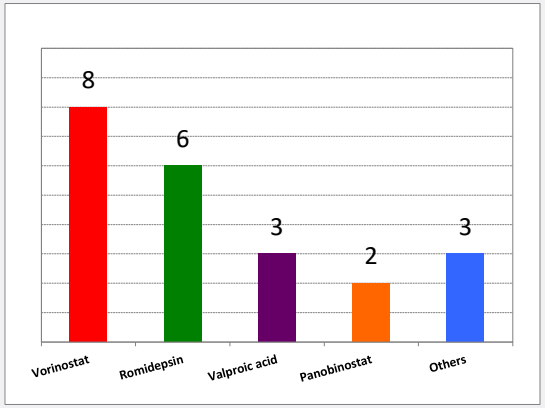
Vorinostat (n=8, 36%)

Romidepsin (n=6, 27%)

Valproic acid (n=3, 14%)

Panobinostat (n=2, 9%)

Others (n=3, 14%)



- ✓ Only **one work** considered CNS outcomes in the study endpoints. Results showed that *vorinostat* did not lead to cognitive decline or neuropsychiatric events.

- ✓ According to ongoing research, no current trial appears to include brain parameters investigating HDACIs.

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Results (II)

HDACI	Group	Target	Study Name	ClinicalTrials.gov Identifier (NCT)/ EudraCT Number/ Status*	Strategy	CNS Assessment	Results
Vorinostat /suberoylanilide hydroxamic acid /SAHA /MK-0683 (VOR)	Hydroxamic acids	Classes I,II & IV	A Phase I/II Investigation of the Effect of Vorinostat (VOR) on HIV RNA Expression in the Resting CD4+ T Cells of HIV-Infected Patients Receiving Stable Antiretroviral Therapy	NCT01319383 Completed	VOR + Stable ART	Yes	- No cognitive decline - No neuropsychiatric events
			A Randomized Study to Compare the Efficacy of Vorinostat/Hydroxychloroquine/Maraviroc (VHM) in Controlling HIV After Treatment Interruption in Subjects Who Initiated ART During Acute HIV Infection	NCT02475915 Completed	VOR + Hydroxychloroquine + Stable ART	No	-
			Research In Viral Eradication of HIV Reservoirs (RIVER)	NCT02336074 EudraCT number: 2014-001425-32 Active, not recruiting	VOR + Stable ART + Vaccines (ChAdV63.HIVconsv [ChAd]; MVA.HIVconsv [MVA])	No	-
			IGHID 11627 - A Phase I Study to Evaluate the Effects of Vorinostat and HIV-1 Antigen Expanded Specific T Cell Therapy (HXTC) on Persistent HIV-1 Infection in HIV-Infected Individuals Started on Antiretroviral Therapy (The XTRA Study)	NCT03212989 Recruiting	VOR + Vaccine (HXTC)+ Stable ART	No	-
			IGHID 11424 - A Pilot Trial of the Effect of Vorinostat and AGS-004 on Persistent HIV-1 Infection (The VOR VAX Study)	NCT02707900 Recruiting	VOR + Vaccine (AGS-004)+ Stable ART	No	-
			A Pilot Study to Assess the Safety and Effect on HIV Transcription of Vorinostat in Patients Receiving Suppressive Combination Anti-retroviral Therapy	NCT01365065 Active, not recruiting	VOR + Stable ART	No	-
			Selective Estrogen Receptor Modulators to Enhance the Efficacy of Viral Reactivation With Histone Deacetylase Inhibitors	NCT03382834 Active, no yet recruiting	VOR + Tamoxifen + Stable ART	No	-
			Combination Latency Reversal With High Dose Disulfiram Plus Vorinostat in HIV-infected Individuals on ART (DIVA): A Single Arm Clinical Trial	NCT03198559 Suspended	VOR + Disulfiram + Stable ART	No	-

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Results (III)

HDACI	Group	Target	Study Name	ClinicalTrials.gov Identifier (NCT)/ EudraCT Number/ Status*	Strategy	CNS Assessment	Results
Romidepsin/ FK228 (RMD)	Depsipeptide	HDAC 1,2,4,6	BIOSKILL: Studying Vacc-4x, an HIV therapeutic vaccine, an assessment of immune-mediated anti-viral effects, when administered with adjuvant GM-CSF prior to HIV latent reservoir activation by the HDAC inhibitor, romidepsin	EudraCT number: 2015-003186-28 Completed	RMD + Vaccine (Vacc-4x) + Adjuvant GM-CSF + Stable ART	No	-
			An Open Phase I/IIa Study to Evaluate the Safety and Effect of Therapeutic HIV-1 Immunization Using Vacc-4x + rhuGM-CSF and HIV-1 Reactivation Using Romidepsin on the Viral Reservoir in Virologically Suppressed HIV-1 Infected Adults on cART (REDUC)	NCT02092116 EudraCT number: 2013-004747-23 Completed	RMD + Vaccine (Vacc-4x; rhuGM-CSF) + Monitored ART Pause	No	-
			A Phase I/II Study of Romidepsin in HIV-Infected Adults With Suppressed Viremia on Antiretroviral Therapy to Assess Safety, Tolerability, and Activation of HIV-1 Expression	NCT01933594 Active, not recruiting	RMD or Placebo (Sodium Chloride) + Stable ART	No	-
			An Open Label Phase I Trial to Evaluate the Safety and Effect of HIVconsv Vaccines in Combination With Histone Deacetylase Inhibitor Romidepsin on the Viral Rebound Kinetic After Treatment Interruption in Early Treated HIV-1 Infected Individuals (BCN02-Romi)	NCT02616874 Completed	RMD + Vaccine (MVA.HIVconsv) + Monitored ART Pause	No	-
			A Phase 2a, Randomized Study of Romidepsin With or Without 3BNC117 to Evaluate the Effects on the HIV-1 Reservoir (ROADMAP)	NCT02850016 Recruiting	RMD + Neutralizing Antibodies (bNAb) + Monitored ART Pause	No	-
			Early Administration of Latency Reversing Therapy and Broadly Neutralizing Antibodies to Limit the Establishment of the HIV-1 Reservoir During Initiation of Antiretroviral Treatment - a Randomized Controlled Trial (eCLEAR)	NCT03041012 Recruiting	RMD + Neutralizing Antibodies (bNAb) + Stable ART or ART Initiation	No	-

Results (IV)

HDACI	Group	Target	Study Name	ClinicalTrials.gov Identifier (NCT)/ EudraCT Number/ Status*	Strategy	CNS Assessment	Results
Valproic acid/ Valproate (VPA)	Short chain fatty acids	Classes I & IIa	Inhibiting Histone Deacetylase: Toward Eradication of HIV	NCT00312546 Completed	VPA + Stable ART	No	-
			10493 - MK-0518 Intensification and HDAC Inhibition in Depletion of Resting CD4+ T Cell HIV Infection	NCT00614458 Completed	VPA + Stable ART	No	-
			Use of Valproic Acid to Purge HIV From Resting CD4+ Memory Cells/ A Proof-of-Concept Study	NCT00289952 *Unknown*	VPA + Stable ART	No	-
Panobinostat/ LBH589	Hydroxamic acids	Classes I & IIa	The Safety and Efficacy of The Histone Deacetylase Inhibitor Panobinostat for Purging HIV-1 From The Latent Reservoir (CLEAR) Study	NCT01680094 Completed	Panobinostat + Stable ART	No	-
			A Phase I-II Pilot Study to Assess the Safety and Efficacy of Combined Administration With Pegylated Interferon-alpha2a and the Histone Deacetylase Inhibitor (HDACi) Panobinostat for Reducing the Residual Reservoir of HIV-1 Infected Cells in cART-Treated HIV-1 Positive Individuals (ACTIVATE)	NCT02471430 Recruiting	Panobinostat + immunomodulatory cytokine Interferon-alpha2a (pegylated IFN-alpha2a) + Stable ART	No	-
Chidamide/ HBI-8000	Benzamide derivatives	Classes I & IIb	Safety and Efficacy of the Histone Deacetylase Inhibitor Chidamide in Combination With Antiretroviral Therapy for Eradication of the Latent HIV-1 Reservoir (CHARTER)	NCT02513901 Completed	Chidamide + Stable ART	No	-
			Efficacy of the Histone Deacetylase Inhibitor Chidamide in Combination With Antiretroviral Therapy for Reactivation of the Latent HIV-1 Reservoir: a Randomized Controlled Clinical Trial	NCT02902185 Active, not recruiting	Chidamide or Placebo + Stable ART	No	-
Sirtuin-1/ SIRT1	NAD-dependent deacetylase sirtuin-1	Class III	Multi Interventional Study Exploring HIV-1 Residual Replication: a Step Towards HIV-1 Eradication and Sterilizing Cure	NCT02961829 Completed	Sirtuin + Stable ART or ART intensification + Dendritic cell vaccine or Auranofin or Nicotinamide	No	-

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CONCLUSIONS

- *Brain outcomes should be considered and assessed in studies testing kick&kill strategies for HIV eradication.*

- *According to published results, only one report investigating HDACIs offers data in the field.*

- *Future trials for HIV cure should consider CNS-related outcomes, not only because of potential detrimental consequences for brain status, but also for possible CNS benefits that could be reached.*

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Thanks for your attention!

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