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# A Novel Bromodomain and Extra-terminal Domain Inhibitors (BETi) that Reverses HIV-1 Latency

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**Presenter Information**

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## **A NOVEL BROMODOMAIN AND EXTRA-TERMINAL DOMAIN INHIBITORS (BETI) THAT REVERSES HIV-1 LATENCY**

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Although combinatory antiretroviral therapy (cART) is effective to reduce HIV-1 viremia, it does not eliminate HIV-1 infection. HIV-1 remains latent with the presence of cART, impeding the cure of AIDS. Recently, latency-reversing agents (LRAs) have been developed to purge latent HIV-1, providing an intriguing strategy for eradication of residual, latent viral reservoirs. Our earlier studies show that antagonism of HIV-1 competitive factor bromodomain containing 4 (BRD4) using bromodomain and extra-terminal domain inhibitor (BETi) JQ1 may facilitate the reversal of HIV-1 latency. BETis have recently emerged as a class of compounds that are promising for both the anticancer and HIV-1 latency-reversing uses. However, the current BETis, including JQ1, are modest to reverse HIV-1 latency as a single drug, which complicates the study of the underlining mechanisms. BETis, which are more potent and easier for synthesis, are currently under active development. UMB-32 is a novel BETi based on an imidazo[1,2-a]pyrazine scaffold. We screened 61 UMB-32 derivatives and identified that one BETi, UMB-136, reactivates HIV-1 in multiple cell models of HIV-1 latency with better efficiency than JQ1 and UMB-32. Furthermore, UMB-136 enhances the latency-reversing effect of PKC activators (Prostratin, Bryostatin) in CD8-depleted PBMCs containing HIV-1 latent reservoirs. Thus, our results illustrate that structurally improved BETis, such as UMB-136, could be use as promising LRAs for HIV-1 eradication.

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