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Linking AZT to ceramide improves its anti-viral action, decreases marrow toxicity and increases brain uptake and retention

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We have synthesized an ester-linked zidovudine (AZT) ceramide prodrug that has a number of therapeutic attributes lacking in AZT. Uptake and retention of AE_6C was greater in cells in culture, indicating that it could serve as a reservoir. For example, after 24 hrs AE_6C was still present, but not free AZT remained and the prodrug still retained its antiviral action. Consistent with that, AE_6C pretreatment reduced infection in cells exposed to Molony murine leukemia virus (M-MuLV) 24 and 48 hrs after drug removal, but not in cells pre-treated with AZT. AE_6C blocked infection as well as AZT when human CD4+ HeLa cells were exposed to the drugs during infection with HIV. AE_6C was much less toxic than AZT to bone marrow erythroid (BFU-E) and myeloid (CFU-GM) hematopoietic progenitors. Given orally, AE_6C attained and retained higher drug concentration in mouse brain and thymus. Thereby providing a prodrug reservoir from which AZT is enzymatically released, which should result in prolonged maintenance of more effective active drug levels. In summary, AE_6C could prove to be a clinically useful drug because it addresses AZT's major limitations. Its grater uptake, retention and prolonged release in cell and target organs may allow lower and less frequent doses of drug to administered, thereby decreasing side effects such as nausea and vomiting, which should increase patient compliance. Because it is less toxic to marrow progenitors, even at equimolar doses, AE_6C is less likely to induce hematopoietic suppression, manifested by anemia, neutropenia, and overall marrow failure.