Background: SAMHD1, a deoxyribonucleoside triphosphate triphosphohydrolase (dNTPase), prevents the infection of blood cells by retroviruses, including HIV, by depleting the cellular dNTP pool available for viral reverse transcription. SAMHD1 is a major regulator of cellular dNTP levels in mammalian cells. Mutations in SAMHD1 are associated with the autoimmune condition Aicardi Goutières Syndrome (AGS), whose clinical manifestations resemble congenital viral infection. The catalytic activity of SAMHD1 is regulated by allosteric binding of dGTP, which enables SAMHD1 monomers/dimers to assemble into the catalytically active tetrameric form.

Conclusions: We have determined the crystal structure of the tetrameric human SAMHD1-dGTP complex. The structure reveals an elegant allosteric mechanism of activation via dGTP-induced assembly of the tetrameric complex from two inactive dimers. Intriguingly, GTP can also activate SAMHD1, and our data further show the binding promiscuity of other dNTPs at the allosteric site. These findings suggest an intricate regulation system that may have a profound effect on the balancing of cellular dNTP pools. These results provide the basis for a mechanistic understanding of SAMHD1 function in HIV restriction, the pathogenesis of AGS, and regulation of cellular dNTP levels.