in peripheral blood mononuclear cells (PBMCs). Drug concentrations achieved in both humanized mice and rhesus macaques were efficacious in suppressing viremia when administered to HIV and SIV infected animals, respectively. PBMCs that were isolated from uninfected monkeys 24 hr after drug administration were refractory to SIV infection. (*Ibid.*)

Currently available drug treatments for HIV infection work in combination to suppress viremia, keeping the virus under control. HIV drug therapy is life-long and strict adherence to treatment regimens is critical to maintain viral suppression, reduce the risk of drug resistance, and minimize the risk of transmission. Efficacious and safe, well-tolerated drugs that are easy to take with low dosing frequency have the potential to improve a patient's adherence and long-term treatment success. For prophylaxis against HIV infection, the only currently available pre-exposure prophylaxis (PrEP) treatment approved by the U.S. Food and Drug Administration is TRUVADA® (emtricitabine/tenofovir DF) for prophylaxis against HIV infection in uninfected people.

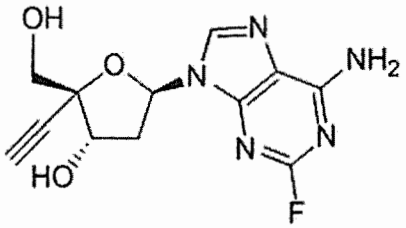
Currently available orally administered anti-retroviral drugs are dosed once-daily. Less frequent dosing may help to alleviate both practical challenges and the cumulative psychological impact of taking daily HIV medications. Long-acting ARTs may potentially help patients return to a greater sense of normalcy and provide flexibility that could impact the way they live, work, travel, relate to others, and see themselves. Additionally, lessons from other chronic diseases requiring life-long treatment such as osteoporosis and type-2 diabetes have shown that some patients adapt to and may prefer once-weekly over once-daily dosing regimens which can result in improved medication adherence.

It would be desirable to have additional prophylactic therapy options for people at risk of HIV infection, either by adminstering a single active agent or a combination of active agents. Additionally, it would be desirable to have oral dosing options for HIV therapies, both for treatment and prophylaxis of HIV infection, that could be administered less frequently than dosing on a daily basis, to provide further alternatives for patients.

SUMMARY

The present disclosure is directed to pre-exposure prophylaxis (PrEP) treatment using 4'-ethynyl-2-fluoro-2'-deoxyadenosine (EFdA) or 4'-ethynyl-2-chloro-2'-deoxyadenosine (ECdA), i.e., use of EFdA or ECdA, or a pharmaceutically acceptable salt or co-crystal of either active agent, for prophylaxis of HIV infection in a subject not infected with HIV who is at risk for said infection. The prophylactic treatment can be via any route or method of administration, including but not limited to administration orally, parenterally or using an implantable composition or device.

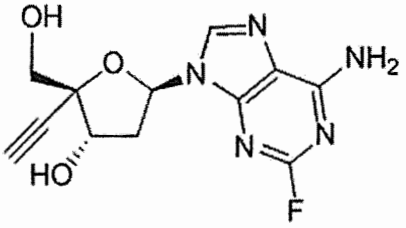
In one aspect, the present disclosure is directed to a compound of structural formula:



or a pharmaceutically acceptable salt or co-crystal thereof,

for use in the inhibition of HIV reverse transcriptase, the treatment of HIV infection, the treatment of AIDS or ARC, the delay in the onset of AIDS or ARC, or the prophylaxis of HIV infection, AIDS or ARC in a subject, wherein the compound or a pharmaceutically acceptable salt or co-crystal thereof is to be administered at a dosing regimen which is less frequent than once-daily.

In another aspect, the present disclosure is directed to use of a compound of structural formula:



or a pharmaceutically acceptable salt or co-crystal thereof, in the manufacture of a medicament for the inhibition of HIV reverse transcriptase, the treatment of HIV infection, the treatment of AIDS or ARC, the delay in the onset of AIDS or ARC, or the prophylaxis of HIV infection, AIDS or ARC in a subject, wherein the compound or a pharmaceutically acceptable salt or co-crystal thereof is to be administered at a dosing regimen which is less frequent than once-daily.

The present disclosure also encompasses treatment of a subject infected with HIV by parenteral administration of EFdA or ECdA, or a pharmaceutically acceptable salt or co-

crystal of either active agent, employing a once-weekly or a less frequent dosing regimen. It further encompasses treatment of a subject infected with HIV by administration of EFdA or ECdA by use of an implantable composition or device which is implanted into the subject once-weekly or less frequently to deliver the active agent during the interval of time from one implant to the subsequent implant.

The present disclosure is further directed to oral administration of EFdA or ECdA, or a pharmaceutically acceptable salt or co-crystal of either active agent, to a subject employing oral dosing regimens for HIV therapy wherein EFdA or ECdA is administered less frequently than once daily. For example, EFdA or ECdA can be orally administered in a dosage regimen of twice-weekly dosing, once-weekly dosing, bi-weekly dosing, twice-monthly dosing, or once-monthly dosing for the the inhibition of HIV reverse transcriptase, treatment of infection by HIV, prophylaxis of infection by HIV, and the prophylaxis, treatment, and/or delay in the onset or progression of AIDS and/or ARC.

DESCRIPTION OF THE FIGURES

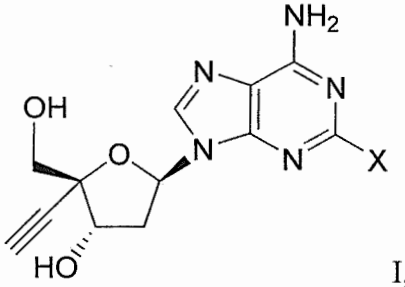
Figure 1 is a graph of viral load changes in SIV-infected monnkeys from the "Once-weekly efficacy in an SIV infected rhesus monkey model of HIV-infection" study described in Example 1.

Figure 2 is a graph of Mean PBMC Concentration versus Time Profiles for EFdA Triphosphate (TP) Following Administration of Once Weekly Oral Doses of EFdA for 3 Weeks to Healthy Fasted Subjects (linear scale) (lower, semi-log plot).

Figure 3 is a graph of Mean EFdA Plasma Concentration versus Time Profiles Following Administration of Once Weekly Oral Doses of EFdA for 3 Weeks to Healthy Fasted Subjects (linear scale, first 24hr post-dose) (lower, semi-log plot) (N=6, LOQ= 3.41 nM).

DETAILED DESCRIPTION OF THE INVENTION

One embodiment of the present invention, referred to herein as Embodiment A, relates to a method for the prophylaxis of HIV infection comprising administering to a subject not infected with HIV an effective amount of a compound of structural Formula I

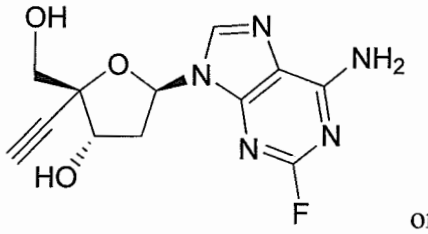


I,

or a pharmaceutically acceptable salt or co-crystal thereof, wherein X is –F or –Cl. An effective amount of said compound may be administered to the subject once-daily, twice-weekly, once-

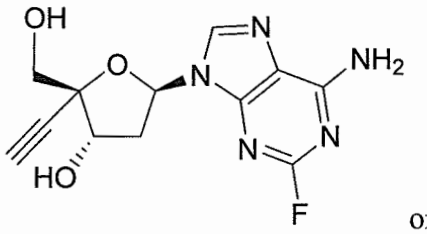
WHAT IS CLAIMED IS:

1. A compound of structural formula:



or a pharmaceutically acceptable salt or co-crystal thereof, for use in the inhibition of HIV reverse transcriptase, the treatment of HIV infection, the treatment of AIDS or ARC, the delay in the onset of AIDS or ARC, or the prophylaxis of HIV infection, AIDS or ARC in a subject, wherein the compound or a pharmaceutically acceptable salt or co-crystal thereof is to be administered at a dosing regimen which is less frequent than once-daily.

2. Use of a compound of structural formula:



or a pharmaceutically acceptable salt or co-crystal thereof, in the manufacture of a medicament for the inhibition of HIV reverse transcriptase, the treatment of HIV infection, the treatment of AIDS or ARC, the delay in the onset of AIDS or ARC, or the prophylaxis of HIV infection, AIDS or ARC in a subject, wherein the compound or a pharmaceutically acceptable salt or co-crystal thereof is to be administered at a dosing regimen which is less frequent than once-daily.

3. The compound of claim 1 or the use of claim 2 for the inhibition of HIV reverse transcriptase, the treatment of HIV infection, the treatment of AIDS or ARC, or delay in the onset of AIDS or ARC, wherein the compound or a pharmaceutically acceptable salt or co-crystal thereof is to be administered orally.

4. The compound or use of claim 3 wherein the subject is human.

5. The compound or use of claim 4, wherein the dosing regimen has a dosing interval range from about once every 3 days to about once per month.

6. The compound or use of claim 5 wherein the dosing regimen is selected from twice-weekly, once-weekly, bi-weekly, twice-monthly or once-monthly.

7. The compound of or use of claim 6 wherein the dosing regimen is once-weekly.

8. The compound or use of claim 7 wherein the dosage amount is from 1 mg to 50 mg at each administration.

9. The compound or use of claim 6 wherein the dosing regimen is bi-weekly or twice monthly.

10. The compound or use of claim 9 wherein the dosage amount is from 2 mg to 100 mg at each administration.

11. The compound or use of claim 6 wherein the dosing regimen is once-monthly.

12. The compound or use of claim 11 wherein the dosage amount is from 4 mg to 200 mg at each administration.

13. The compound or use of claim 3 wherein the compound or a pharmaceutically acceptable salt or co-crystal thereof is to be administered parenterally.

14. The compound or use of claim 13 wherein the subject is human.

15. The compound or use of claim 14 wherein the dosing regimen is once-weekly, bi-weekly, twice-monthly, once-monthly, once-quarterly, twice-yearly, once-yearly, once every 18 months or bi-annually.

16. The compound or use of claim 15 wherein the compound or a pharmaceutically acceptable salt or co-crystal thereof is to be administered by infusion, by an implantable drug delivery composition or by inhalation spray.

17. The compound or use of claim 16 wherein the compound or a pharmaceutically acceptable salt or co-crystal thereof is to be administered by infusion and the dosing regimen is once-weekly, bi-weekly, twice-monthly, once-monthly, once-quarterly, twice-yearly or once-yearly.

18. The compound or use of claim 16 wherein the compound or a pharmaceutically acceptable salt or co-crystal thereof is to be administered by an implantable drug delivery composition and the dosing regimen is once-quarterly, twice-yearly, once-yearly, once every 18 months or bi-annually.

19. The compound or use of claim 16 wherein the compound or a pharmaceutically acceptable salt or co-crystal thereof is to be administered by inhalation spray.

20. The compound of claim 1 or the use of claim 2 for the prophylaxis of HIV infection, AIDS or ARC.

21. The compound or use of claim 20 wherein the subject is human.

22. The compound or use of claim 21 wherein the compound or a pharmaceutically acceptable salt or co-crystal thereof is to be administered orally.

23. The compound or use of claim 22 wherein the dosing regimen is once-daily, twice-weekly, once-weekly, bi-weekly, twice-monthly or once-monthly

24. The compound or use of claim 23 wherein the dosing regimen is twice-weekly, once-weekly, bi-weekly, twice-monthly or once-monthly.

25. The compound or use of claim 20 wherein the compound or a pharmaceutically acceptable salt or co-crystal thereof is to be administered parenterally.

26. The compound or use of claim 25 wherein the dosing regimen is once-weekly, bi-weekly, twice-monthly, once-monthly, once-quarterly, twice-yearly, once-yearly, once every 18 months or bi-annually.

27. The compound or use of claim 25 wherein the compound or a pharmaceutically acceptable salt or co-crystal thereof is to be administered by infusion and the dosing regimen is once-weekly, bi-weekly, twice-monthly, once-monthly, once-quarterly, twice-yearly or once-yearly.

28. The compound or use of claim 27 wherein the compound or a pharmaceutically acceptable salt or co-crystal thereof is to be administered by an implantable drug delivery composition and the dosing regimen is once-quarterly, twice-yearly, once-yearly, once every 18 months or bi-annually.