Executive Summary

Project title:

An exploratory study of pharmacologic measure of tenofovir diphosphate and emtricitabine triphosphate in dried blood spots as adherence testing for monitoring pre-exposure prophylaxis (MSS276R)

Objectives

The objectives of this project are:

1. To explore the feasibility of antiretroviral drugs detection of tenofovir-diphosphate (TFV-DP)/emtricitabine-triphosphate (FTC-TP) in dried blood spot (DBS) for adherence testing
2. To compare the performance of antiretroviral drug detection in plasma and DBS
3. To discriminate gradients of adherence to pre-exposure prophylaxis

Project design

An exploratory pharmacological study

Target population

HIV-infected patients and individuals at-risk for HIV infection on daily tenofovir disproxil fumarate (TDF)/emtricitabine (FTC).

Methods

Paired plasma-DBS samples were collected from 34 HIV-infected patients and 59 HIV-uninfected at-risk individuals. Comparison of detectability of TFV-DP/FTC-TP in DBS with tenofovir (TFV)/FTC in plasma was assessed on 220 paired plasma-DBS samples from 93 study subjects. Measurement of drug levels of TFV/FTC in plasma, and TFV-DP/FTC-TP in DBS were performed by liquid chromatography/tandem mass spectrometry.

Main achievements

The performance of pharmacologic exposure of TFV-DP/FTC-TP in DBS was comparable with the measurement of TFV/FTC exposure in plasma samples. Concordance of TFV/FTC in plasma with TFV-DP/FTC-TP was observed in 193/220 (87.7%) samples.

Among HIV-infected patients receiving daily TDF/FTC, the TFV concentrations in plasma ranged from 10.8 to 247 ng/mL (mean concentration: 54.4 ng/mL) and the FTC concentrations ranged from 24.2 to 2000 ng/mL (mean concentration: 624.0 ng/mL). Based on DBS analyses, patients had a mean TFV-DP concentration of 7662.2 fmol/punch and a

mean FTC-TP concentration of 19.9 pmol/punch.

Among HIV-uninfected individuals, after TDF/FTC initiation, the mean plasma concentrations at 2 weeks, 12 weeks, 28 weeks, and >12 months for TFV were 145.3 ng/mL, 162.7 ng/mL, 161 ng/mL, 128.9 ng/mL, respectively, and for FTC were 533.7 ng/mL, 764.8 ng/mL, 702.8 ng/mL, 384.1 ng/mL, respectively. In DBS, all individuals had detectable TFV-DP and FTC-TP exposure at 2 weeks, 12 weeks, 28 weeks, and >12 months.

Of 25 paired plasma-DBS samples obtained from HIV-uninfected individuals during the washout phase (between days 0-14 after stopping TDF/FTC), when both TFV/FTC in plasma were below the limit of quantification of 10 ng/mL (n=23), TFV-DP concentrations in DBS were all within the quantifiable range (100% of the samples and over a longer period of 14 days after the last dose), whereas FTC-TP were detectable in 60.9% (14/23) of the samples obtained within 2 to 10 days after the last dose (FTC-TP levels ranged between 0.8 to 3.5 pmol/punch).

Conclusions

This project demonstrated the feasibility of utilizing DBS as alternative biological sample for detecting TDF/FTC exposure and is useful for adherence testing. The pharmacologic measurement of detectable TFV-DP in DBS would serve as a biomarker of long-term exposure to TDF/FTC and adherence, whereas FTC-TP in DBS indicates a recent dosing.

項目名稱

探索使用乾血點作為測試愛滋病抗逆轉錄酶病毒藥物替諾福韋/恩曲他濱以助監察接觸前預防性投藥的服藥依從性 (MSS276R)

目標

1. 評估使用乾血點樣本作為測試愛滋病抗逆轉錄酶病毒藥物替諾福韋和恩曲他濱的可行性，以助檢測服藥依從性
2. 對比血液和乾血點樣本作愛滋病抗逆轉錄酶病毒藥物的可檢測性
3. 區分接觸前預防性投藥的服藥依從性

項目設計

藥理學探索性研究

目標人群

服用替諾福韋/恩曲他濱的愛滋病感染者及風險較高而沒有受感染人士

方法

收集了 34 名愛滋病病毒感染者和 59 名沒有感染愛滋病病毒的風險較高人士的配對血液和乾血點樣本。在這 93 名研究者的 220 對血液和乾血點樣本上，評估了乾血點樣本中二磷酸替諾福韋/三磷酸恩曲他濱與血液中替諾福韋/恩曲他濱的可檢測性的比較。通過液相色譜法-質譜聯用法測量血液中替諾福韋/恩曲他濱和乾血點樣本中的二磷酸替諾福韋/三磷酸恩曲他濱的藥物檢測性。

主要結果

乾血點樣本中二磷酸替諾福韋/三磷酸恩曲他濱的藥物檢測性與血液中替諾福韋/恩曲他濱的表現能有效地互相比較。在 193/220 (7.7%) 樣本中觀察到替諾福韋/恩曲他濱在血液中與二磷酸替諾福韋/三磷酸恩曲他濱的一致性。

於愛滋病病毒感染者中，血液中的替諾福韋濃度範圍為 10.8 - 247 ng/mL (平均濃度：54.4 ng/mL)，恩曲他濱濃度範圍為 24.2 - 2000 ng/mL (平均濃度：624.0 ng/mL)。基於乾血點樣本分析，患者的二磷酸替諾福韋平均濃度為 7662.2 fmol/punch，恩曲他濱平均濃度為 19.9 pmol /punch。

於沒有感染愛滋病病毒的人士中，開始服用替諾福韋/恩曲他濱後，替諾福韋的第 2 週，12 週，28 周和 >12 個月的平均血液濃度為 145.3 ng/mL，162.7 ng/mL，161 ng/mL 和 128.9 ng/mL; 對於恩曲他濱，則分別為 533.7 ng/mL，764.8 ng/mL，702.8 ng/mL 和 384.1 ng/mL。在乾血點樣本中，所有人士均可檢測到第 2 週，12 週，28 週，和 > 12 個月的二磷酸替諾福韋/三磷酸恩曲他濱。

停止服用替諾福韋/恩曲他濱後 0 - 14 天之內，於沒有感染愛滋病病毒的人士中的 25 對配對血液和乾血點樣本中，於 23 名研究者中發現，當血液的替諾福韋/恩曲他濱濃度均低於 10 ng/mL 的定量限時，乾血點樣本中的二磷酸替諾福韋/三磷酸恩曲他濱濃度均在可量化範圍內 (100% 的樣本和最後一次服用後 14 天) ，而在最後一次用藥後 2 - 10 天內采集的樣本中，60.9% (14/23) 樣本可檢測到三磷酸恩曲他濱 (三磷酸恩曲他濱濃度介於 0.8 - 3.5 pmol /punch)。

結論

是次項目顯示使用乾血點能有效地檢測服用愛滋病抗逆轉錄酶病毒藥物替諾福韋和恩曲他濱，及其作為接觸前預防性投藥的服藥依從性。以藥理學測量方法檢驗出乾血點中的二磷酸替諾福韋可表示為長期服用接觸前預防性投藥，而三磷酸恩曲他濱可代表最近服用指標。