Raltegravir-based post-exposure prophylaxis (PEP): a safe, well-tolerated alternative regimen
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Interest in the ‘Test and Treat’ strategy for HIV prevention among men who have sex with men living in Bangkok
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HIV-infection during treatment of a chronic hepatitis B virus infection: implications for PrEP?
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Raltegravir based post exposure prophylaxis (PEP): A safe, well tolerated alternative regimen

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BACKGROUND
Three-drug regimens are routinely recommended in the UK for PEP after high-risk exposure to HIV. The current Department of Health & British Association for Sexual Health & HIV first-line regimen is lopinavir / ritonavir, tenofvir & emtricitabine (truvada). Raltegravir based regimens may be used as an alternative (raltegravir & truvada). This is a review of the use of raltegravir containing PEP to identify why & when this is initiated and its tolerability & safety compared to first-line PEP.

AIM
To identify when raltegravir is being used as PEP and compare tolerability & safety of first line PEP regimens with raltegravir containing regimens.

METHOD
Pharmacy records identified patients who received raltegravir based PEP & matched controls who received standard PEP during the same period. Relevant information was gathered from patients’ notes. Local PEP guidelines recommend three appointments with a healthcare professional (HCP); Day 1-5, day 14 and day 28.

RESULTS: Resistance profile
All switches to raltegravir-containing PEP due to the genotypic resistance profile of the contact took place by day 3 of the course. (Figure 1)

RESULTS: Intolerance
In the matched control group taking first line PEP, 3/33 (9%) experienced a ALT rise. 2 patients who initiated first line PEP were switched to raltegravir based PEP due to significant ALT rise. 0/19 who initiated on raltegravir based PEP experienced a significant ALT rise. There was no significant renal toxicity seen in either group.

RESULTS: Adherence
Self reported adherence was higher in patients who were initiated on Raltegravir based PEP:
•51% of patients matched control group reported at least one late or missed dose (n=33)
•26% of patients who initiated on raltegravir based PEP reported at least one late or missed dose (n=19)

RESULTS:Seroconversion
One patient who started first-line PEP was found to be HIV positive at baseline. An MSM who received raltegravir-containing PEP seroconverted 4.5 months after the course of PEP. He reported 3 episodes of unsafe sexual behaviour since completing PEP. None of the other patients are known to have seroconverted.

Discussion
• Prevention strategies including novel use of ARVs (PEP, Pre exposure prophylaxis & treatment for prevention) to reduce HIV incidence are becoming more important.
• This small single centre observational study suggests that Integrase inhibitors (Raltegravir) may be useful alternatives to first line PEP
• This study is however limited as is small & retrospective: larger randomised clinical trials are now needed.
• Use of newer agents e.g. integrase inhibitors may be limited by access and cost.

Key Findings
• Raltegravir based PEP appears to be better tolerated than first line PEP.
• ALT rises were seen in first line PEP but not in patients initiated on raltegravir based PEP.
• No renal toxicity was seen in either group.
• Patients who switched to raltegravir based PEP reported an improvement in tolerability.
• Higher adherence was reported in patients who initiated raltegravir based PEP.
• There were no unexplainable HIV seroconversions in patients on raltegravir based PEP.

RESULTS: Hepatic/Renal Toxicity
In the matched control group taking first line PEP, 3/33 experienced a ALT rise. 2 patients who initiated first line PEP were switched to raltegravir based PEP due to significant ALT rise. 0/19 who initiated on raltegravir based PEP experienced a significant ALT rise. There was no significant renal toxicity seen in either group.

RESULTS: Intolerance
Switching due to drug intolerance was largely due to gastrointestinal side effects between days 1 to 16. (Figure 2)

REPORTED side effects for patients who initiated raltegravir-containing PEP were lower compared to the matched control group: 10/19 (53%) patients on raltegravir-containing PEP reported no side effects by day 28 treatment compared to 5/33 (15%) patients in the matched control group. (Figure 3,4)

12/14 (79%) patients who were switched to raltegravir-containing PEP reported improvement in their side effects by their next appointment

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**Background**

- The current HIV epidemic in Thailand is primarily driven by new cases among men who have sex with men (MSM) [1].
- In Bangkok, HIV prevalence among MSM increased from 17.3% in 2003 to 24.7% in 2008 [2].
- A multinational, randomized, controlled trial (National Institutes of Health HTN052) demonstrated 96% risk reduction for antiretroviral therapy (ART) as prevention of genetically linked HIV-1 incident transmissions in HIV-discordant heterosexual couples [3].
- As a result, universal HIV testing and immediate ART (Test and Treat) has emerged as a strategy to reduce HIV transmission in certain at-risk populations including HIV-serodiscordant couples, female sex workers (FSWS), MSM, and people who inject drugs (PWID) [4].

**Methods**

- This is a cross-sectional study conducted among MSM clients who attended the HIV voluntary counseling and testing (VCT) service at the Thai Red Cross Anonymous Clinic in Bangkok, Thailand, from August 2011 to March 2012.
- MSM participants were asked to complete a set of self-administered questionnaires “prior to the pre-test counseling session” and “after the post-test counseling session”.
- Prior to the pre-test counseling session, participants were asked about previous HIV testing behaviors and viral risk factor modification after knowing HIV status, attitudes toward regular HIV testing, attitudes toward immediate ART and intention to take ART immediately if tested HIV-positive.
- After the post-test counseling, participants who tested HIV-negative were asked again about attitudes toward regular HIV testing. Participants who tested HIV-positive were asked the same questions regarding the attitudes toward immediate ART and intention to take ART immediately.
- Results of HIV testing and other sexually transmitted infections were gathered through the clinic database system.
- The study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

**Results**

**Characteristics of MSM clients attending VCT service (Table 1).**

- **Previous HIV testing behaviors:**
  - HIV testing was reported by 69.2%; 31.2% had HIV testing once.
  - 46.8% had tested for 2-5 times.
  - 8.2% had tested for 6-10 times.
  - 13.9% had tested for > 10 times.
  - The most common reasons for previous HIV testing included perceived risk behaviors (71%), annual health checkup (29.4%), and partner’s request (15.4%).
  - One-third of cases previously having negative result repeated HIV testing to confirm the accuracy.

**Table 1. Characteristics of MSM clients attending VCT service at the Thai Red Cross Anonymous Clinic in Bangkok, Thailand.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Anti-HIV positive</th>
<th>Anti-HIV negative</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQ) years</td>
<td>27 (22-31.5)</td>
<td>26 (22-31)</td>
<td>0.8</td>
</tr>
<tr>
<td>Educational levels: High school or lower</td>
<td>42.9%</td>
<td>47.6%</td>
<td></td>
</tr>
<tr>
<td>Bachelor’s degree or higher</td>
<td>37.1%</td>
<td>51.5%</td>
<td>0.49</td>
</tr>
<tr>
<td>Marital status: Single</td>
<td>86.9%</td>
<td>80%</td>
<td>0.38</td>
</tr>
<tr>
<td>Transsexual (%)</td>
<td>0%</td>
<td>0.9%</td>
<td>1.0</td>
</tr>
<tr>
<td>HIV infection (N=121)</td>
<td>6.5%</td>
<td>6.4%</td>
<td>1.0</td>
</tr>
<tr>
<td>Syphilis (N=113)</td>
<td>6.5%</td>
<td>3.3%</td>
<td>0.38</td>
</tr>
<tr>
<td>Gonorrhea (N=112)</td>
<td>22.6%</td>
<td>11.1%</td>
<td>0.11</td>
</tr>
</tbody>
</table>

**Attitudes toward universal HIV testing and immediate ART among MSM clients prior to receiving HIV pre-test counseling (Table 2).**

- Of 246 MSM, 83.6% agreed that HIV testing should be done universally, 9.9% thought HIV testing should be done only among individuals with behavioral risks, and 3% thought HIV testing should be included as part of the annual health checkup program. Only 0.8% disagreed with the regular HIV testing policy and 9.9% had no comment on the policy.

**Table 2. Previous HIV testing and attitudes toward regular HIV testing and immediate ART among MSM clients (N=246).**

<table>
<thead>
<tr>
<th>Pre-test questions</th>
<th>All volunteers N=342</th>
<th>HIV-infected volunteers N=53</th>
<th>Volunteers with HIV-anxiety negative N=290</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously planned for HIV testing</td>
<td>36.7%</td>
<td>18.7%</td>
<td>39.6%</td>
<td>0.053</td>
</tr>
<tr>
<td>Ever had anti-HIV-ART</td>
<td>70.2%</td>
<td>50%</td>
<td>74.7%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Behavioral risk reduction, if previously tested negative</td>
<td>69%</td>
<td>63.3%</td>
<td>70%</td>
<td>0.465</td>
</tr>
<tr>
<td>Regular HIV testing</td>
<td>40%</td>
<td>50%</td>
<td>38.3%</td>
<td>0.23</td>
</tr>
<tr>
<td>Committing sex with interest to join a program which will provide regular HIV testing</td>
<td>77.8%</td>
<td>84.9%</td>
<td>76.5%</td>
<td>0.18</td>
</tr>
<tr>
<td>Interest to join a program which will provide immediate ART if tested HIV-positive</td>
<td>85.8%</td>
<td>90%</td>
<td>84.9%</td>
<td>0.38</td>
</tr>
</tbody>
</table>

**Table 3. Attitudes toward universal HIV testing and immediate ART among MSM before and after learning their HIV-negative and positive status.**

**Conclusions**

- Prior to receiving pre-test counseling, 77.8% expressed their interest to join a program that will ask people to come for regular HIV testing. The testing frequency most selected was only when risk perceived (51.5%), followed by twice a year (17.7%), and once every year (14%). Health benefits from testing (63%), free testing (38.6%), and speedy service (37.7%) were the most common persuasive reasons for coming to regular HIV testing.

- Interest to join a program which will provide immediate ART if tested HIV-positive was indicated by 85.8% of MSM. Longevity (77.2%), prevention of HIV transmission to others (61.4%), having responsibility to take care of others (40.4%) were the common reasons for interest in immediate ART if tested positive program. Costs (41.4%), life-long burden (41.1%) and drug side effects (32.2%) were cited as main barriers to immediate ART.

**Figure 1. Common barriers to have immediate ART**

- Cell phone is the most feasible way to use among the volunteers for further notification among HIV-negative and positive volunteers (75.4% and 86.7%, respectively).
- The use of short messaging services (SMS) in healthcare is the most common choice to use for contact tracing and partner notification among the volunteers (48.3%).

**References**


**Implications**

- Interest to join in a program which will provide regular HIV testing was very high among MSM who were VCT clients in Bangkok. The interest increased among HIV-negative MSM after learning their status through post-test counseling service.
- More than 85% of MSM also expressed interest to join an immediate ART program if tested HIV-negative. Among MSM who finally learned that they had HIV-positive status, the interest increased strongly.
- Personal health benefit was the most commonly cited reasons both for the interest in regular HIV testing and the interest in immediate ART, while almost 2/3 of MSM also indicated HIV prevention as a reason to take immediate ART. Costs and time needed to spent for these services were the main concerns. These factors should be taken into consideration when planning for HIV communication and service delivery system for a Test and Treat program among MSM.
Introduction

The application of Tenofovir disoproxil fumarate (TDF) with or without Emtricitabine (FTC) as pre-exposure prophylaxis (PrEP) may prevent HIV transmission. However, the protective effect of TDF-based PrEP differed significantly among clinical studies [1-3], and PrEP-failure always bears the risk of inducing resistance-associated mutations due to continued exposure to antiretroviral drugs. As TDF-based PrEP might be frequently used after FDA approval, it is important to identify factors influencing PrEP-efficacy and to quantify the risk of the development of PrEP-associated resistance mutations [4]. However, so far only poor adherence was shown to be associated with PrEP-failure [1-3] and the number of reported PrEP-assocated resistance mutations is limited. Here we report the detection of TDF-resistant HIV in a Patient that acquired an HIV-infection despite monitored good adherence to a TDF-therapy of a chronic Hepatitis B Virus (HBV) infection.

Case Presentation

Routine screening for sexually transmitted infections (STI) revealed a chronic Hepatitis B virus (HBV) infection of a 25-year old MSM who was treated for an early syphilis. Due to very high HBV-DNA titers (1.78 x 10^7 IU/ml) a therapy with TDF was initiated immediately. Under TDF therapy HBV-DNA titers dropped below the detection limit within 10 months, documenting the simultaneously detectable (K65K/R in the genotypic resistance profile, Fig. 2). Retrospective analyses of frozen serum samples detected HIV-seroconversion 12 months prior to diagnosis (Table 1; A62A/V, K65R).

Discussion

The TDF therapy of a chronic HBV infection in this case resembles a PrEP with TDF that should be protective against HIV infection [2]. There are several reasons that might explain the “PrEP-failure”:

- Lack of adherence: unlikely
- Missed or delayed treatment: unlikely
- Transmission of K65R is extremely rare [5,6].
- Low HBV/RNA levels document a substantial effect of TDF, especially as the HLA type does not indicate, that the patient is an “elite controller” (Table 1; 7.B).

Concomitant STI

- STI damage the mucosal barrier [10].
- HIV-infection during treatment of a chronic Hepatitis B – implications for PrEP?

Conclusions

TDF/FTC has recently been approved by the FDA as PrEP against HIV for individuals with high-risk sexual behavior. However, this case suggests that concomitant STI – a considerable problem for individuals with high-risk sexual behavior – may compromise the protective effect of TDF-based PrEP. Additionally, this case illustrates the risk to induce resistance related mutations when HIV infections remain unrecognized for a prolonged time. Thus, TDF-based PrEP cannot replace but only expand other protective measures against HIV and individuals receiving PrEP must be closely monitored for PrEP failure.

References


Fig. 1: Quantification of HBV and HIV virus load and concomitant STI. A) Course of HBV-DNA levels. X-axis crosses y-axis at lower limit of detection (357 IU/ml). B) Concomitant STI: Syphilis: CT: Proctitis with Chlamydia trachomatis, GO: Gonorrhea.

Fig. 2: Resistance analysis

Table 1: HIV type

<table>
<thead>
<tr>
<th>HLA Class I</th>
<th>before Diagnosis</th>
<th>after Diagnosis</th>
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<tr>
<td>HLA-A</td>
<td></td>
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<tr>
<td>HLA-B</td>
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<td></td>
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<tr>
<td>HLA-C</td>
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