HIV Drug Therapy GLASGOW 2012

PRE- AND POST-EXPOSURE PROPHYLAXIS AND TREATMENT AS PREVENTION

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Raltegravir based post exposure prophylaxis (PEP): A safe, well tolerated alternative regimen

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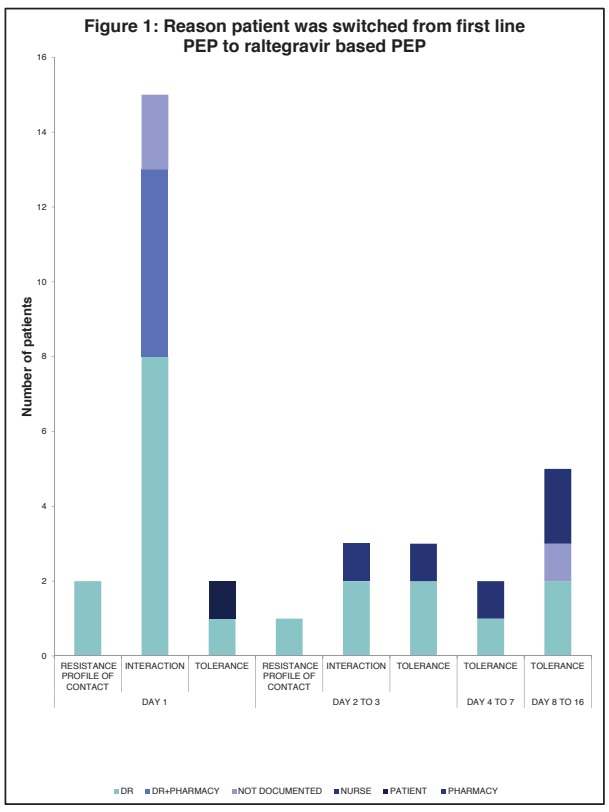
BACKGROUND
Three-drug regimens are routinely recommended in the UK for PEP after high-risk exposure to HIV. The current Department of Health & British Association for Sexual Health & HIV first-line regimen is lopinavir / ritonavir, tenofovir & emtricitabine (truvada). Raltegravir based regimens may be 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.

Figure 1: Reason patient was switched from first line PEP to raltegravir based PEP



RESULTS
Between February 2010 to April 2012, 509 courses of PEP were prescribed; 33 (6.5%) were raltegravir-based PEP; 33 matched controls were identified during the same period.

•18/33 (54%) were initiated due to potential drug-drug interactions with ritonavir.

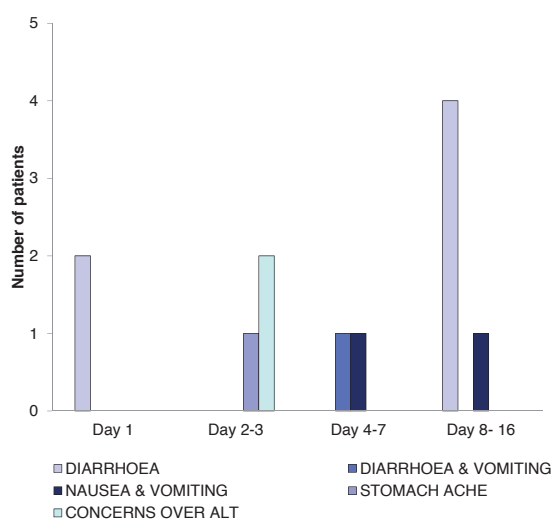
•3/33 (10%) were initiated due to the resistance profile of the contact

•12/33 (36%) were switched due to intolerance of first-line regimen

RESULTS: Drug-drug interactions

All switches to raltegravir-based PEP due to drug-drug interaction occurred by day 3 of the regimen, with 15/18 (83%) switching on day 1 of treatment. Potential drug-drug interactions included inhaled steroids such as fluticasone, herbal therapies (St Johns wort), isotretinoin, anti depressants and anti psychotics. Doctors initiated the majority of these switches, identifying the largest proportion of significant drug-drug interactions. (Figure 1)

Figure 2: Intolerance which caused switch from first line PEP to raltegravir based PEP



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)

Figure 3: Side effects reported by patients who were initiated on raltegravir based PEP (n=19)

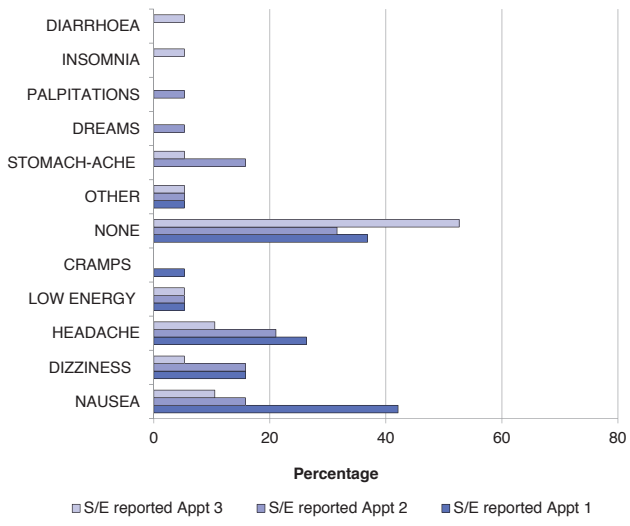
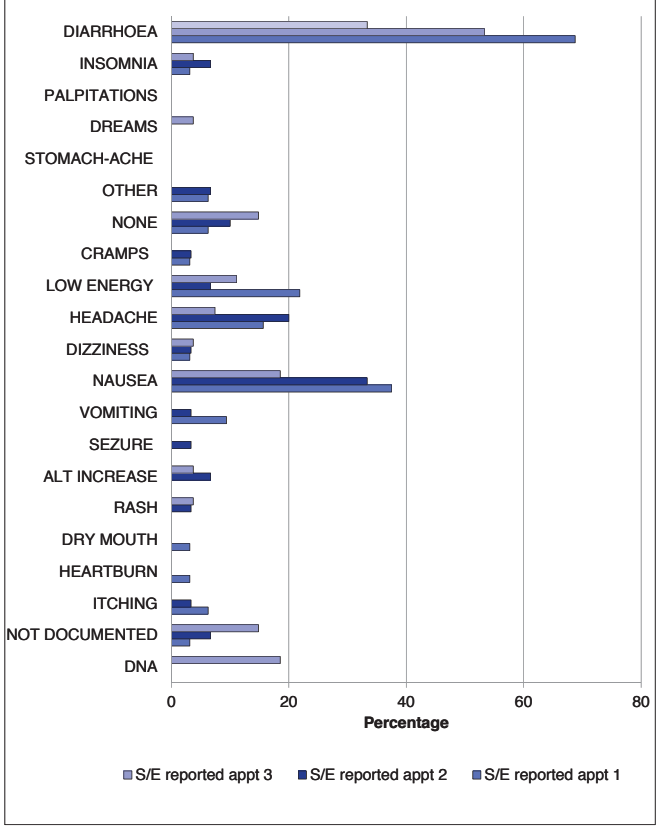


Figure 4: Reported side effects of the matched control group who initiated standard PEP (n=33)



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

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.**

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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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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 2009.[2]
- A multinational, randomized, controlled trial (National Institutes of Health HPTN052) demonstrated 96% risk reduction for antiretroviral therapy (ART) as prevention of genetically linked HIV-1 incident transmissions in HIV-serodiscordant 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]
- The acceptability of the Test and Treat strategy among Thai MSM is unknown.

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-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 and behavioral risk 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

- Previous 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.

Variables	Anti-HIV positive	Anti-HIV negative	P values
Median age (IQR): years	27 (22-31.5)	26 (22-31)	0.8
Educational levels: High school or lower	42.9%	47.6%	
Bachelor's degree or higher	37.1%	51.5%	0.49
Marital status: Single	86.4%	80%	0.35
Transsexual (%)	0%	0.5%	1.0
HBV infection (N=121)	6.5%	6.4%	1.0
Syphilis (N=113)	6.5%	3.33%	0.38
Genital wart (N=121)	22.6%	11.1%	0.11

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 0.6% 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=342)

Pre-test questions	All volunteers N=342	HIV-infected volunteers N=53	Volunteers with HIV-antibody negative N=289	P-value*
Previously planned for HIV testing	36.7%	18.75%	39.6%	0.053
Ever had anti-HIV negative	70.2%	50%	74.7%	<0.0001
Behavioral risk reduction, if previously tested negative	69%	63.33%	70%	0.465
Regular HIV testing	40%	50%	38.3%	0.23
Committing sex service	13.6%	8.8%	14.4%	0.58
Interest to join a program which will provide regular HIV testing	77.8%	84.9%	76.5%	0.18
Interest to join a program which will provide immediate ART (if tested HIV-positive)	85.8%	90.4%	84.9%	0.38
Ability to get partner(s) to come for HIV testing	57.5%	61.5%	57.1%	0.55

*comparison between the volunteers with anti-HIV positive and negative

- 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 to come for 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.

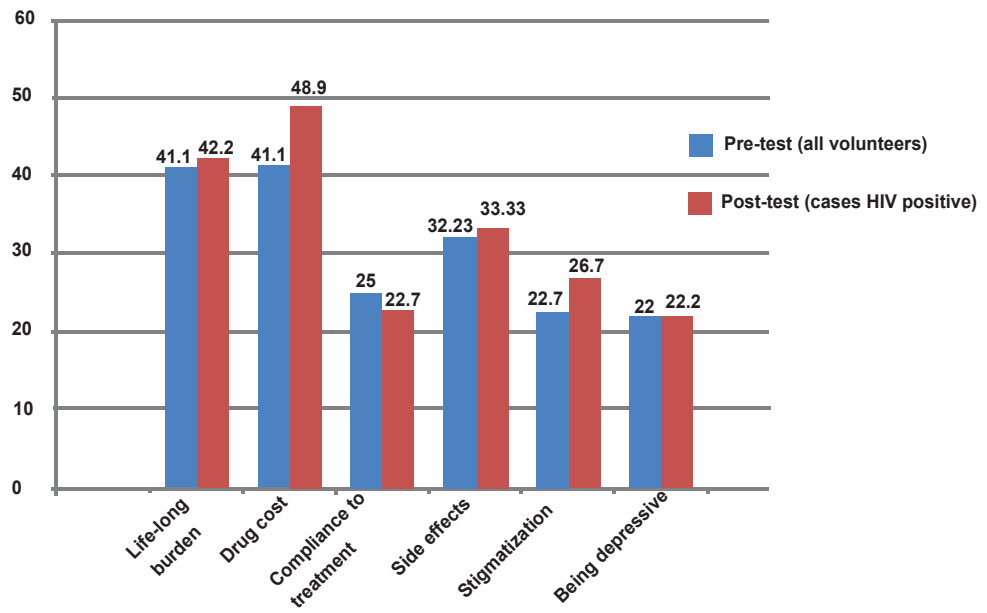
Attitudes toward universal HIV testing and immediate ART among MSM after learning their HIV-negative and HIV-positive status

- Among MSM who tested HIV-positive (n=45, 13.2%), the interest to participate in an immediate ART program remained high compared to the interest prior to knowing their HIV-positive status (93.3 vs 86.7%, p=0.371).
- Among HIV-negative MSM, the interest to participate in a regular HIV testing program significantly increased after knowing their HIV-negative status (83.4% vs 77.0%, p<0.001).

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

Regular HIV testing	MSM who tested HIV-negative (N=233) Pre-test	Post-test	P-value
Agree with policy for VCT	96.5%	98.7%	0.103
Interest to join a regular HIV testing program	77.0%	83.4%	<0.0001
Immediate ART	**MSM who tested HIV-positive (N=45) Pre-test**	**Post-test**	**P-value**
Wish to take immediate ART ≥80%	71.1%	84.4%	<0.0001
Interest to join an immediate ART program	86.7%	93.3%	0.37

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 health care is the most common choice to use for contact tracing and partner notification among the volunteers (48.3%).

CONCLUSION

- 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-positive. Among MSM who finally learned that they had HIV-positive status, the interest remained high.
- 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 public communication and service delivery system for a Test and Treat program among MSM.

REFERENCES

1. The Analysis and Advocacy Project (A2). The updated Asian Epidemic Model (AEM) Projections for HIV/AIDS in Thailand 2005-2025. Nonthaburi: Family Health International (FHI) and Bureau of AIDS, TB and STIs, Department of Disease Control, Ministry of Public Health, Thailand, 2008. Print.
2. Kladsawas K, van Griensven F, Wimonsate W, Varangrat A, Smutraprapoot P, Kittinunvorakul C, et al. Trends in HIV prevalence and risk behavior among men who have sex with men (MSM) in Bangkok, Thailand, 2003 to 2009 Abstract. XVIII International AIDS Conference, Vienna, Austria, 18-23 July 2010.
3. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011;365:493-505.
4. Delva W, Eaton JW, Meng F, Fraser C, White RG, Vickerman P, et al. HIV treatment as prevention: optimising the impact of expanded HIV treatment programmes. PLoS Med 2012;9:e1001258.

HIV-Infection during treatment of a chronic Hepatitis B Virus infection – implications for PrEP?

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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 an 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-associated 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.

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; S: Syphilis; CT: Proctitis with *Chlamydia trachomatis*; GO: Gonorhea. *Note that GO was diagnosed 2 months before HIV-serology became positive. C) HIV-RNA levels and HIV serology. Before HIV-diagnosis, HIV-RNA was quantified in frozen serum samples retrospectively. Orange HIV-Serology results identify retrospective analyses of frozen serum samples. X-axis crosses y-axis at lower limit of detection (37 copies/ml).

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 good therapy adherence of the patient (Fig. 1A). However, the patient did not change his risky sexual behavior as he suffered from numerous STI during the TDF-therapy (Fig. 1B).

After negative HIV tests at the beginning of the TDF treatment and six months later, no routine HIV-tests were performed until an HIV-infection (subtype b) was confirmed during a syphilis re-infection 30 months later. At this point, TDF-resistant and TDF-susceptible HIV were 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 and low HIV-RNA levels from seroconversion to diagnosis (always <400 copies/ml; Fig. 1C). A combined antiretroviral therapy with RTV-boosted DRV, TDF and FTC was initiated and HIV-RNA levels dropped below the lower detection limit within 2 months. TDF was continued in spite of proven HIV TDF-resistance as treatment of the chronic HBV infection.

Substitutions in RT gene (relative to HXB2)

A62A/V, **K65K/R**,
K102Q, D121D/H, I135T, E169D/E, G196E/G, Q207E,
L214F, V245M/V

Geno 2 Pheno®

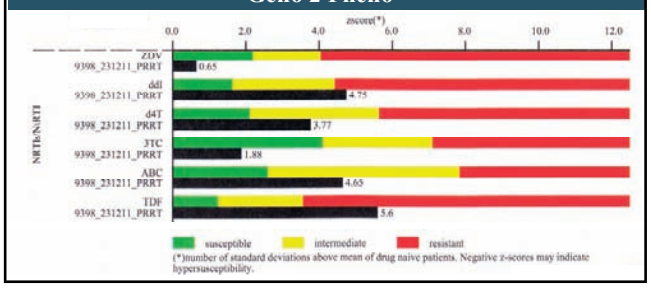

Fig. 2: Resistance analysis

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 •The fast drop and subsequent uninterrupted suppression of HBV-DNA is an excellent marker for good therapy adherence.
Transmitted drug resistance	Unlikely •Transmission of K65R is extremely rare [5,6]. •Loss of K65R during TDF exposure is very unlikely. •Continuously low HIV-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; [7,8]).
Lack of PrEP efficacy	Possible •TDF Mono-PrEP was as effective as TDF/FTC in one study [2]. In other settings TDF/FTC was significantly more protective [4]. •However, TDF-levels in the anal mucosa are high and should therefore protect MSM who practice receptive anal intercourse [9].
Concomitant STI	Likely •STI damage the mucosal border [10]. •STI increase the number of HIV-susceptible cells in the mucosa [10]. •2 months before seroconversion GO was diagnosed (Fig. 1B and C).

HLA class I		
HLA-A	*33.03	*68:01
HLA-B	*08:01	*44:03
HLA-C	*07:02	*07:06

Table 1: HLA type

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

[1] **Grant, R. M., Lama, J. R., Anderson, P. L., McMahan, V., Liu, A. Y., Vargas, L., Goicochea, P., et al.,** Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010. **363:** 2587-2599.
[2] **Baeten, J. M., Donnell, D., Ndase, P., Mugo, N. R., Campbell, J. D., Wangisi, J., Tappero, J. W., et al.,** Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med* 2012. **367:** 399-410.
[3] **Van Damme, L., Corneli, A., Ahmed, K., Agot, K., Lombaard, J., Kapiga, S., Malahleha, M., et al.,** Preexposure prophylaxis for HIV infection among African women. *N Engl J Med* 2012. **367:** 411-422.
[4] **van der Straten, A., Van Damme, L., Haberer, J. E. and Bangsberg, D. R.,** Unraveling the divergent results of pre-exposure prophylaxis trials for HIV prevention. *AIDS* 2012. **26:** F13-F19.
[5] **SPREAD programme,** Transmission of drug-resistant HIV-1 in Europe remains limited to single classes. *AIDS* 2008. **22:** 625-635.
[6] **Bartmeyer, B., Kuecherer, C., Houareau, C., Werning, J., Keeren, K., Somogyi, S., Kollan, C., et al.,** Prevalence of transmitted drug resistance and impact of transmitted resistance on treatment success in the German HIV-1 Seroconverter Cohort. *PLoS One* 2010. **5:** e12718.
[7] **Migueles, S. A. and Connors, M.,** Long-term nonprogressive disease among untreated HIV-infected individuals: clinical implications of understanding immune control of HIV. *JAMA* 2010. **304:** 194-201.
[8] **Pereyra, F., Jia, X., McLaren, P. J., Telenti, A., de Bakker, P. I. W., Walker, B. D., Ripke, S., et al.,** The major genetic determinants of HIV-1 control affect HLA class I peptide presentation. *Science* 2010. **330:** 1551-1557.
[9] **Patterson, K. B., Prince, H. A., Kraft, E., Jenkins, A. J., Shaheen, N. J., Rooney, J. F., Cohen, M. S. and Kashuba, A. D. M.,** Penetration of tenofovir and emtricitabine in mucosal tissues: implications for prevention of HIV-1 transmission. *Sci Transl Med* 2011. **3:** 112re4.
[10] **Fox, J. and Fidler, S.,** Sexual transmission of HIV-1. *Antiviral Res* 2010. **85:** 276-285.