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Commentary

Pre-exposure chemoprophylaxis of HIV infection: Quo vadis?

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ABSTRACT

The pre-exposure chemoprophylaxis (now commonly referred to as PrEP) of HIV infection has gained increased momentum, concomitantly with the successful use of combination drug regimens for the treatment of AIDS. A pivotal component in the current drug combination regimens for the treatment of AIDS as well as the ongoing PrEP trials is tenofovir disoproxil fumarate (TDF, Viread®) and its combination with emtricitabine (FTC). The combination of TDF with FTC has been marketed as Truvada®. TDF and TDF/FTC has proven effective, if orally administered daily or intermittently, in the prevention of rectal simian human immunodeficiency virus (SHIV) infection in macaques. Topical tenofovir gel has proven effective in the prevention of HIV infection in women in South Africa. Oral TDF/FTC has proven effective in the prevention of HIV infection in men having sex with men, and recent press releases divulged that oral TDF/FTC is also effective in preventing HIV infection in serodiscordant couples in Botswana, Kenya and Uganda. Other PrEP studies are still ongoing. Available data point to the efficacy and safety of TDF with or without FTC in the prophylaxis of HIV infection (AIDS).

1. Introduction

Little progress has been made over the past years towards the development of an effective vaccine against human immunodeficiency virus (HIV). Laudable vaccination attempts, i.e. with the ALVAC and AIDSVAX, effected only modest efficacy, scored as 31.2% at best [1]. This contrasts with the success obtained with the drug combination therapy for HIV infection, which is limited only by its cost, the requirement of lifelong adherence, and the unknown effects of long-term (in principle, life-long) treatment [2].

In 2006, I proposed that, based on (i) the original observations of Tsai et al. [3] that simian immunodeficiency virus (SIV) infections in macaques could be completely prevented by (*R*)-PMPA (tenofovir) and (ii) the favorable safety/efficacy profile that over the past 5-year period (2001–2006) had been established for tenofovir disoproxil fumarate (TDF, Viread®) in the treatment of AIDS (HIV infection), TDF should be strongly recommended for the chemoprophylaxis of HIV infections in humans [4]. In an Editorial, Grant and Wainberg [5] supported this suggestion, thereby advocating caution when moving forward.

In the meantime, we are 5 years down the road, and accruing evidence has ascertained that TDF (Viread®) and its combination with emtricitabine (Truvada®) are indeed effective in the pre-exposure chemoprophylaxis of HIV infection, as has been demonstrated in both experimental models [simian human immunodeficiency virus (SHIV) infection and a number of large human trials]. The only problem has been implementation of, and adherence to the prophylactic use of the drugs. The importance of adherence to HIV microbicides has been underscored in particular by Ferrer et al. [6]. Development of drug resistance has not proven to be an issue, since the best way to prevent drug resistance is to prevent HIV infection entirely, which is actually the aim of pre-exposure prophylaxis (PrEP) [5].

2. Historical background

Emanating from a collaboration between Antonin Holý (Czechoslovak Academy of Sciences in Prague) and myself that had started in 1976, we described in 1986 [7] the broad-spectrum antiviral activity of the acyclic nucleoside phosphonate (*S*)-HPMPA [(*S*)-9-(3-hydroxyl-2-phosphonylmethoxypropyl)adenine], which, while not commercialized itself, would serve as the prototype of this class of compounds. The antiviral activity spectrum of its cytosine counterpart (*S*)-HPMPC was described in 1987 [8], and this compound would be later commercialized as cidofovir (Vistide®) (in 1996) for the treatment of CMV retinitis in AIDS patients. Concomitantly with (*S*)-HPMPA, we also described PMEA [adefovir, 9-(2-phosphonylmethoxyethyl)adenine] as an antiretroviral agent [7] (further described *in extenso* by Pauwels et al. [9]). PMEA would later (in 2002) be approved as adefovir dipivoxil (Hepsera®) for the treatment of chronic hepatitis B.

The principle of chirality as present in (*S*)-HPMPA was retained in the design of new analogues of (*S*)-HPMPA, namely (*R*)-FPMPA

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[10] and (*R*)-PMPA [11]. The latter was approved by the US FDA in 2001 as tenofovir disoproxil fumarate (TDF) (Viread®) for the treatment of AIDS (HIV infection) and 7 years later (in 2008) for the treatment of hepatitis B. Tenofovir disoproxil (as a prodrug of tenofovir) was first described by Robbins et al. [12] and Naesens et al. [13]. TDF would (in 2004) be launched as a fixed-dose double drug combination (termed Truvada®) with emtricitabine and (in 2006) as a fixed-dose triple drug combination (termed Atripla®) with emtricitabine and efavirenz. Recently approved (in 2011) was a fixed-dose triple drug combination (Complera™, Eviplera®) of TDF with emtricitabine and rilpivirine (TMC278). All these TDF-based fixed-dose drug combinations (whether Truvada®, Atripla® or Complera™) are intended for the therapy of AIDS (HIV infection) and are administered orally as a single daily pill. A forthcoming, also TDF-based fixed-dose drug combination, for treatment of AIDS, is the Quad pill containing four active ingredients, TDF, emtricitabine, elvitegravir and cobicistat, which should be launched in 2012 (for recent references on rilpivirine, elvitegravir and combicistat, see [14–16]). The active ingredients that are part of these fixed-dose drug combinations act as either NtRTI (nucleotide reverse transcriptase inhibitor: TDF), NRTI (nucleoside reverse transcriptase inhibitor: emtricitabine), or NNRTI (non-nucleoside reverse transcriptase inhibitor: efavirenz or rilpivirine), INI (integrase inhibitor: elvitegravir) or "booster" (pharmacoenhancer: cobicistat) (Fig. 1).

3. Chemoprophylaxis of experimental HIV or SIV infections in macaques

Within 2 years after its discovery as an antiretroviral agent [11], Tsai et al. [3] demonstrated that tenofovir [(*R*)-PMPA] could completely block SIV infection in macaques, if the compound was administered subcutaneously, starting 48 h before, or 4 or 24 h after intravenous SIV inoculation (Fig. 2) [3]. If, however, treatment with tenofovir was begun at 48 or 72 h after virus inoculation, effectiveness of tenofovir in preventing a persistent SIV infection was reduced [17].

HIV-2 infection in macaques could be completely prevented by tenofovir when administered subcutaneously 12 or 36 h after intravaginal HIV-2 inoculation [18]. In newborn macaques inoculated with SIV by 3 days of age, tenofovir, when administered subcutaneously at 2 doses of 4 mg/kg either 4 h before or 20 h after, 1 and 24 h after, or as a single dose of 30 mg/kg at 1 h after SIV inoculation, completely prevented the infection [19]. These data indicate that one or two doses of tenofovir may protect human newborns against intrapartum HIV infection.

In fact, the data published by Tsai et al. [3], Otten et al. [18] and Van Rompay et al. [19], taken together, suggest that tenofovir may completely prevent retrovirus infections irrespective of the route by which they are transmitted, i.e. parenteral, sexual or perinatal. Van Rompay et al. further suggested that prophylactic administration of tenofovir in newborns and adults would still be beneficial even to prevent infections with viral variants possessing reduced susceptibility to tenofovir [20].

4. Chemoprophylaxis of experimental SHIV infections in macaques

Oral tenofovir disoproxil fumarate (TDF) provided partial protection against SHIV infection in a stringent monkey model, where the virus (SHIV 3F162p3) was inoculated intrarectally once weekly for 14 weeks or until a macaque became infected, and the compound was given through the food. The study was hampered by the small number of animals used and the variability in blood levels of TDF resulting from the oral dosing. Control animals became infected after receiving a median of 1.5

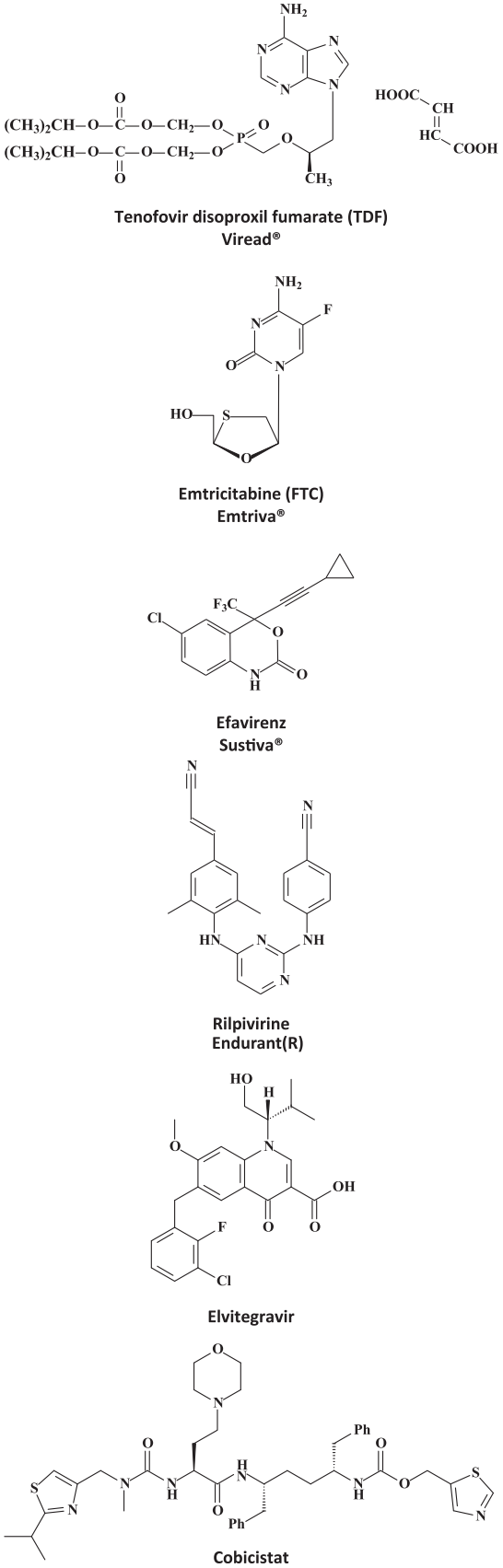

Fig. 1. Structures of TDF, FTC, efavirenz, rilpivirine, elvitegravir and cobicistat. Viread® = TDF. Truvada® = TDF + emtricitabine. Atripla® = TDF + emtricitabine + efavirenz. Complera™ = TDF + emtricitabine + rilpivirine. Quad = TDF + emtricibatine + elvitegravir + cobicistat.

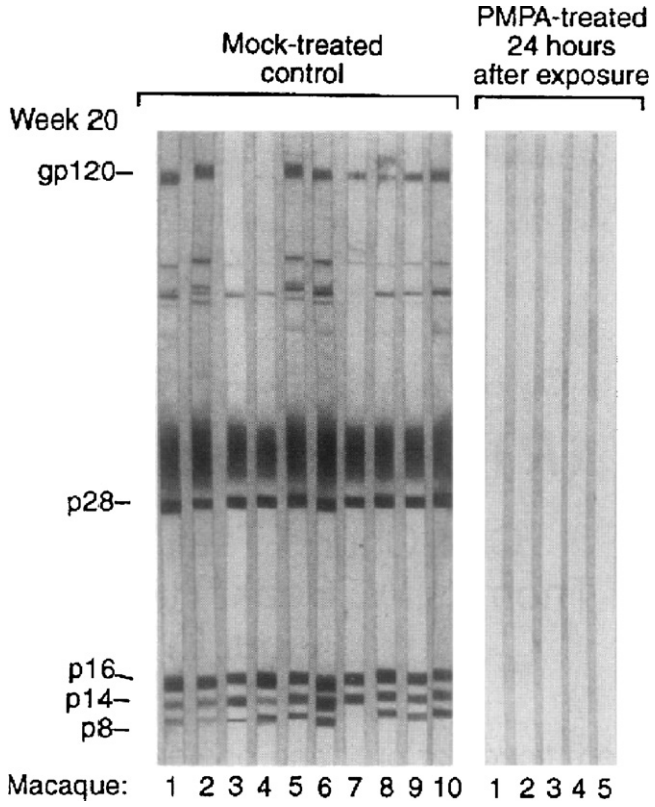

Fig. 2. Protein immunoblot analysis of SIV-specific antibody response in macaques 20 weeks post infection with SIV. Mock-treated control macaques ($n = 10$) and macaques treated with PMPA (tenofovir) starting at 24 h post infection ($n = 5$) are presented. Antibodies to *env* glycoprotein gp120, *gag* proteins p28, p16 and p8 and *vpx* protein p14 were detected in all of the control macaques. None of the macaques treated with PMPA starting 24 h post infection showed SIV-specific antibodies. According to Tsai et al. [3].

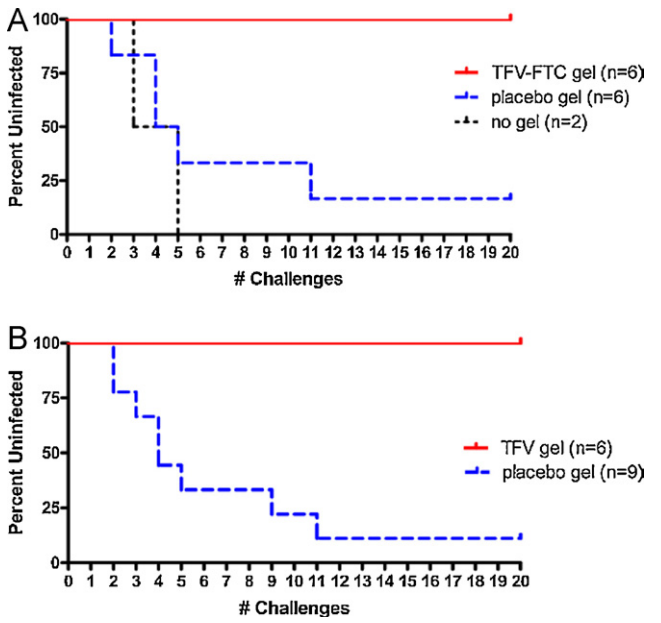

Fig. 3. Gel with TFV–FTC combination or TFV alone fully protects macaques against vaginal $SHIV_{SF162P3}$ infection. The Kaplan–Meier curves show data on the number (#) of twice-weekly challenges with 10 $TCID_{50}$ of $SHIV_{SF162P3}$ and the number of uninfected macaques. (A) TFV–FTC gel. The differences in infection between the TFV–FTC gel arm and the placebo gel arm were statistically significant ($P = 0.004$; log rank test). (B) TFV gel. The differences in infection between the TFV group and the placebo gel group were statistically significant ($P = 0.001$; log rank test). According to Parikh et al. [22].

virus inoculations, macaques receiving TDF daily (1 animal remained uninfected after 14 inoculations) and those receiving TDF weekly became infected after a median duration of 6.0 and 7.0 weeks, respectively [21].

More dramatic results were obtained in macaques that were infected intravaginally, twice weekly, with SHIV (SF162p3) for a total of 20 exposures: a pre-exposure vaginal application gel with 1% tenofovir alone or in combination with 5% emtricitabine afforded complete protection, whereas with the placebo gel virtually 90% of the animals became infected (Fig. 3). The authors, Parikh et al. [22] concluded that topical gel containing tenofovir alone or combined with emtricitabine can provide highly effective topical prophylaxis, overcoming the need for noncoital use [22].

5. Pre-exposure prophylaxis (PrEP)

According to Grant et al. [23], PrEP (pre-exposure prophylaxis) research was first proposed in 2001, before the advent of a global response for providing antiretroviral therapy [24]. It was predicted that HIV PrEP research, built on partnership between sponsors, investigators, communities and governments, and requiring the cooperation among such diverse interests, would not be easy [23].

A case in point was the trial set up in Cambodia to determine whether daily oral tenofovir disoproxil fumarate (TDF) was safe and effective in preventing the sexual transmission of HIV infection: this trial was stopped in August 2004 and never resumed [25]. A similar trial set up in Nigeria was discontinued as well.

Opposition to these PrEP trials (which were sponsored by Family Health International (FHI)) reached its nadir with the dramatic protest action at the Gilead Booth at the XV International AIDS Conference 2004 in Bangkok, Thailand [26]. Singh and Mills pointed out that "if tenofovir would someday proven to be clinically effective as a PrEP, today's (2005 !) irresponsible reporting and activism surrounding tenofovir could cause those in need to snub the drug if or when, it becomes licensed for use as a PrEP" [26]. Lange in the same issue [27] warned that "we must not let protestors, representing only a tiny minority, derail PrEP trials".

If widely implemented, PrEP should come on top of other prevention strategies (such as counseling and condom campaigns) and not as a substitution [28].

PrEP should be distinguished from post-exposure prophylaxis (PEP) which is based on a short (generally 28-day) course of antiretroviral therapy initiated as soon as possible after a high-risk exposure [29]. Post-exposure prophylaxis with zidovudine is assumed to be protective, i.e. after percutaneous (needle stick) exposure to HIV [30]. In the earlier days, zidovudine given ante partum and intra partum to the mother and to the newborn for 6 weeks was shown to reduce the risk of maternal–infant HIV transmission [31].

6. Tenofovir gel as an HIV-1 microbicide

After tenofovir gel had been found safe and effective in preventing HIV-1 infection in PBMCs and explant cultures [32], Abdool Karim described the effectiveness and safety of tenofovir gel in the prevention of HIV infection in women [33]. In this CAPRISA 004 study, tenofovir gel reduced acquisition of HIV by 39% overall (Fig. 4), by 54% in women with high gel adherence (>80%); by 38% in women with intermediate gel adherence (50–80%) and still by 28% in women with low gel adherence (<50%) [33]. The authors concluded that tenofovir gel could potentially fill an

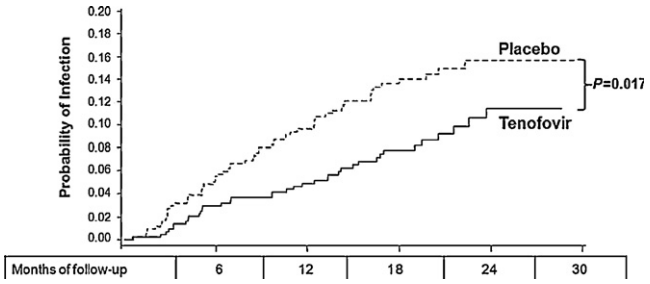

Fig. 4. Kaplan–Meier estimates of cumulative probability of HIV infection in the tenofovir and placebo gel arms. The Table provides the cumulative number of HIV endpoints, corresponding HIV incidence rates, and effectiveness of tenofovir gel for each additional 6 months of follow-up. According to Abdool Karim et al. [33].

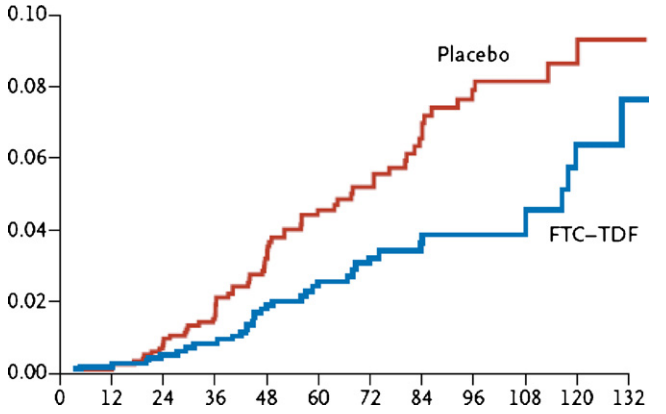

Fig. 5. The efficacy of preexposure prophylaxis with emtricitabine and tenofovir disoproxil fumarate (FTC–TDF) was 44%, as compared with placebo ($P = 0.005$). The cumulative probability of HIV acquisition is shown for the two study groups. The inset graph shows a more detailed version of the overall graph up to a probability of 0.10. According to Grant et al. [35].

important HIV prevention gap, especially for women unable to successfully negotiate mutual monogamy or condom use.

7. Oral TDF or TDF/FTC for prevention of HIV infection

The first clinical study with oral TDF in the prevention of HIV infection in women was inconclusive, owing to the premature closures of the Cameron and Nigeria study sites. Yet, the data gathered from the Ghana study still indicated that while the effectiveness of oral TDF (daily dose: 300 mg) could not be conclusively assessed because of the too small number of HIV infections observed during the study (eight seroconversions occurred: two in the PDF group and six in the placebo group, a difference which did not achieve statistical significance [34]), daily oral dose of TDF in HIV-uninfected women was not associated with increased clinical or laboratory adverse events [34].

In the iPrEx study of 3324 person-years (2499 HIV-seronegative men or transgender women who have sex with men (MSM)) randomly assigned to receive either (oral) placebo or a combination of oral TDF/FTC [35], 100 became infected with HIV during the follow-up (median, 1.2 years, maximum, 2.8 years), 36 in the TDF/FTC group and 64 in the placebo group. This means a 44% reduction in the incidence of HIV in the TDF/FTC group, as compared to the placebo group (Fig. 5) [35].

At the recent IAS (International AIDS Conference) held in Rome, July 17–20, 2011, final iPrEx analysis confirmed PrEP effectiveness for MSM. PrEP with Truvada® was 42% effective in an overall intent-to-treat analysis, but, among participants with detectable drug in their blood, PrEP with Truvada® was 92% effective, demonstrating very high efficacy in people who were adherent to the study protocol [36].

Details of the iPrEx study were reported at the IAS 2011, Rome, 17–20 July 2011. Taken together, they point to the efficacy of Truvada® in PrEP of HIV infection [37–39].

Abdool Karim and Baxter [40] and Willyard [41] reviewed the different trials of HIV pre-exposure prophylaxis (PrEP) that have been planned (Fig. 6). The iPrEx study has in the meantime been completed. The result(s) of the "Botswana" (US Centers for Disease Control) and the "Kenya and Uganda" Partners PrEP study (University of Washington, Seattle) have already been the subject of preliminary press releases (see *infra*) and those of the other studies (VOICE study, FEMPrEP, "Thailand" study) still have to be divulged. The FEMPrEP study was stopped pending an in-depth analysis.

8. Intermittent PrEP

Meanwhile, intermittently dosed PrEP (i.e. twice weekly, as opposed to daily) has been suggested as a possible HIV prevention strategy (i.e. in men having sex with men, twice weekly) [42].

In the rectal SHIV transmission model in macaques, an intermittent prophylaxis regimen of TDF combined with FTC (emtricitabine) offered complete protection, if administered only 2 h before and 24 h after such weekly challenge [43] (Fig. 7).

In the rectal SHIV infection model in macaques, the combination of TDF with FTC given 1, 3 or 7 days before exposure followed by a second dose 2 h after exposure was as protective as daily drug administration. A two-dose regimen initiated 2 h before or after virus exposure was effective and full protection was achieved by simply doubling the drug concentration of TDF/FTC [44]. Intermittent prophylaxis with TDF/FTC would strengthen the possibility of developing feasible, cost-effective strategies to prevent HIV transmission in humans.

9. New recently completed and still ongoing PrEP studies

The VOICE (*V*aginal and *O*ral *I*nterventions to *C*ontrol the *E*pidemic) study is the first study to compare the safety and efficacy of oral *versus* topical PrEP for prevention of sexual transmission of HIV. VOICE is designed as a five-arm, double-blinded study in which women are first randomized to receive either gel or oral PrEP, and then within each group, randomly assigned to either tenofovir 1% topical gel or placebo gel, or to oral TDF, oral Truvada® (FTC/TDF) or oral placebo. The study will enroll 4200 women at various study sites in Africa [45].

According to a press release from the Centers of Disease Control (CDC), the TDF2 study showed that TDF/FTC (Truvada®) reduced the risk of acquiring HIV infection by roughly 63% in the study population of uninfected heterosexual men and women. Overall a total of 1290 HIV-uninfected heterosexual male and female participants in Botswana were enrolled in the TDF2 trial and randomly assigned to take a daily TDF/FTC pill or a placebo pill. Among the 601 individuals who received TDF/FTC, there were nine who became infected with HIV during the study. Among the 599 individuals who received placebo, 24 became infected with HIV. This translates into a statistically significant overall reduction in risk of 62.6% [46].

The Partners PreEP study led by the University of Washington's International Clinical Research Center, involved 4758 HIV serodiscordant couples (in which one partner has HIV and the other does not), carried out at nine research sites in Kenya and Uganda. Through 31 May 2011, a total of 78 HIV infections occurred in the study, 18 among those assigned to TDF, 13 among those assigned to TDF/FTC, and 47 among those assigned to placebo. Thus, those

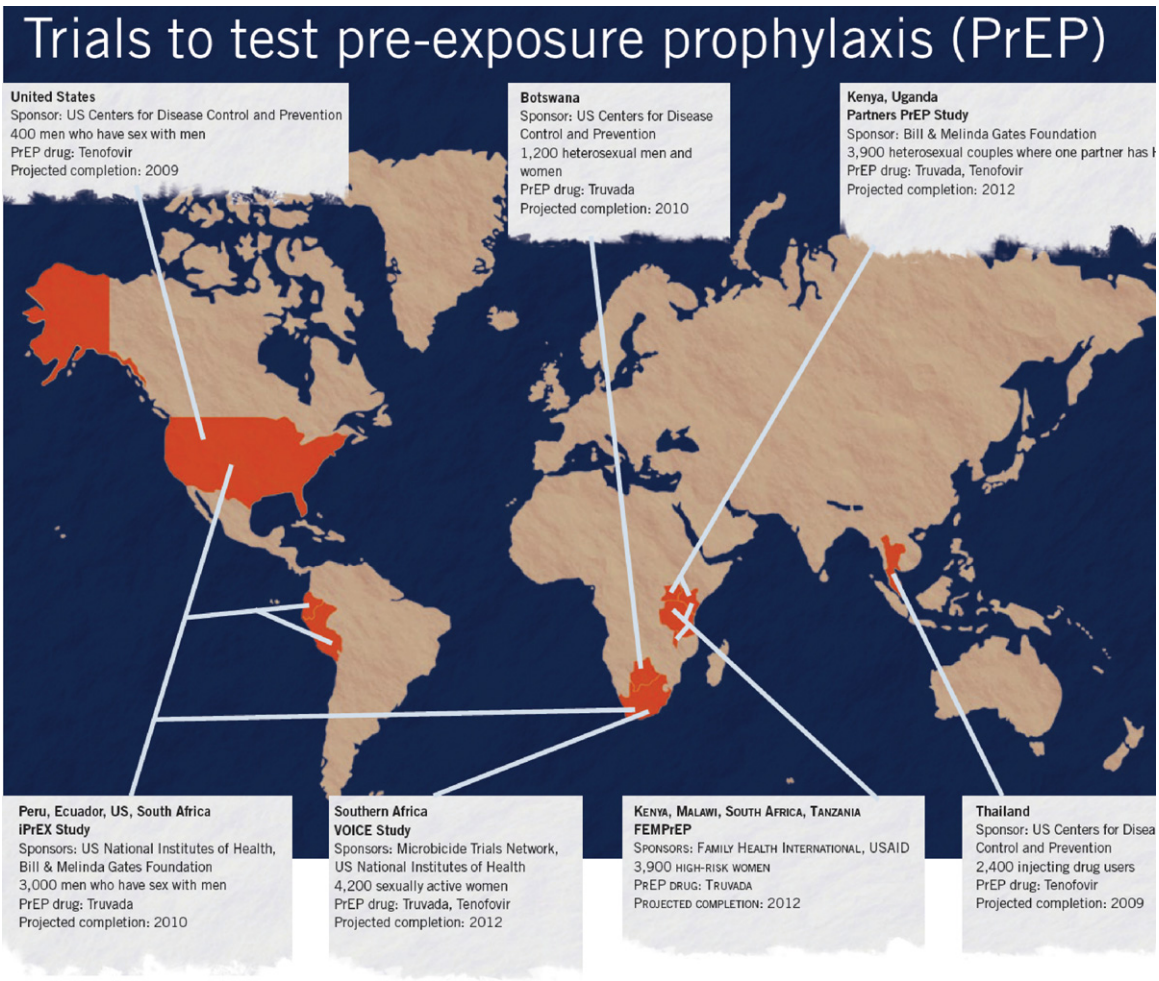

Fig. 6. Trials to test pre-exposure prophylaxis (PrEP). According to Willyard [41].

who received TDF had an average of 62% fewer HIV infections, and those who received TDF/FTC had 73% fewer HIV infections than those who received placebo [47].

In the Partners PrEP study all participants received a comprehensive package of HIV prevention services, which included intensive safer sex counseling, HIV testing, free condoms, testing and treatment for sexually transmitted infections, and monitoring and care for HIV infection. In the study, adherence to the daily PrEP medication was very high, more than 97% if the study medications were taken. The Partners PrEP study is the first to show that PrEP reduces HIV risk in heterosexual men and women. Results from the full panel of completed and ongoing studies of PrEP will together provide decisive information on the ultimate prevention benefits of PrEP in different populations [48].

10. Conclusions and perspectives

In 2009, 25 years after the discovery of HIV, 25 compounds had been approved by the US FDA for the treatment of HIV infection (AIDS) [49], with the recent approval of rilpivirine (TMC 278, Endurant®), the current score is 26. As a rule, these drugs are used in combination regimens, one of the most prominent drugs used as

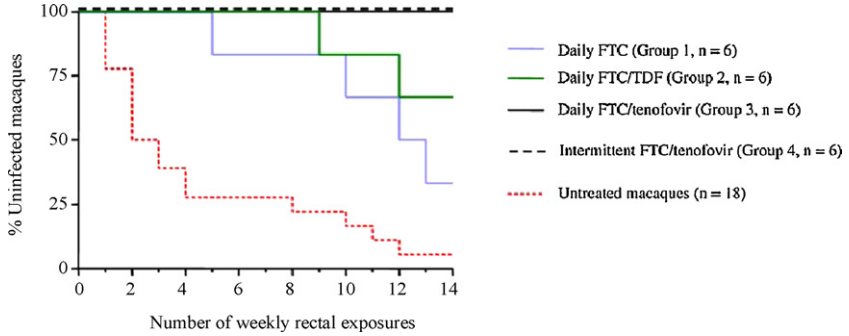

Fig. 7. Protection against repeated rectal virus exposures by daily or intermittent PrEP. Each survival curve represents the cumulative proportion of uninfected macaques as a function of the number of weekly rectal exposures. Protected animals in groups 1–4 remained negative after a mean washout out of 27 weeks (range, 17–60 weeks). According to García-Lerma et al. [43].

such (Viread®) or in combination (Truvada®, Atripla®, Complera™, Eviplera® or the Quad pill expected for 2012) being TDF. Of key importance in these treatment regimens is the acyclic nucleoside phosphonate tenofovir [50]. Tenofovir attests to the magic of the phosphonate bond present in tenofovir [51].

With the accruing number of PrEP trials shown to be safe and effective, the implementation programs will require substantial resources with extensive community education about the indications, availability and effectiveness of the intervention [40]. The concern about drug resistance is not a serious issue, as the best way to prevent HIV drug resistance is to prevent the HIV infection altogether.

Separately from the ethical and public health issues compounding PrEP there are the questions of the formulation (topical *vs.* oral PrEP?) and dosing (daily *vs.* intermittent PrEP?) and the composition (TDF, TDF/FTC, or any other drug combination?). Oral TDF or TDF/FTC would have the advantage over topical (i.e. vaginal) application that it could be used in the prevention of any HIV infection, irrespective of its route of transmission, whether sexual (intravaginal, intrarectal, peroral), parenteral or perinatal. In principle, oral TDF or TDF/FTC should also be effective in the prevention of HBV (hepatitis B virus) infection as well.

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References

[1] Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, et al. MOPH-TAVEG investigators. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med 2009;361:2209–20.
[2] Richman DD, Margolis DM, Delaney M, Greene WC, Hazuda D, Pomerantz RJ. The challenge of finding a cure for HIV infection. Science 2009;323:1304–7.
[3] Tsai C-C, Follis KE, Sabo A, Beck TW, Grant RF, Bischofberger N, et al. Prevention of SIV infection in macaques by (R)-9-(2-phosphonylmethoxypropyl)adenine. Science 1995;270:1197–8.
[4] De Clercq E. The role of tenofovir in the prevention of HIV infections. AIDS 2006;20:1990–1.
[5] Grant RM, Wainberg MA. Chemoprophylaxis of HIV infection: moving forward with caution. J Infect Dis 2006;194:874–6.
[6] Ferrer RA, Morrow KM, Fisher WA, Fisher JD. Toward an information–motivation–behavioral skills model of microbicide adherence in clinical trials. AIDS Care 2010;22:997–1005.
[7] De Clercq E, Holý A, Rosenberg T, Sakuma T, Balzarini J, Maudgal PC. A novel selective broad-spectrum anti-DNA virus agent. Nature 1986;323:464–7.
[8] De Clercq E, Sakuma T, Baba M, Pauwels R, Balzarini J, Rosenberg I, et al. Antiviral activity of phosphonylmethoxyalkyl derivatives of purine and pyrimidines. Antiviral Res 1987;8:261–72.
[9] Pauwels R, Balzarini J, Schols D, Baba M, Desmyter J, Rosenberg I, et al. Phosphonylmethoxyethyl purine derivatives: a new class of anti-human immunodeficiency virus agents. Antimicrob Agents Chemother 1988;32:1025–30.
[10] Balzarini J, Holý A, Jindrich J, Dvorakova H, Hao Z, Snoeck R, et al. 9-[(2RS)-3-fluoro-2-phosphonylmethoxypropyl] derivatives of purines: a class of highly selective antiretroviral agents in vitro and in vivo. Proc Natl Acad Sci U S A 1991;88:4961–5.
[11] Balzarini J, Holý A, Jindrich J, Naesens L, Snoeck R, Schols D, et al. Differential antiherpesvirus and antiretrovirus effects of the (*S*) and (*R*) enantiomers of acyclic nucleoside phosphonates: potent and selective *in vitro* and *in vivo* antiretrovirus activities of (*R*)-9-(2-phosphonomethoxypropyl)-2,6-diaminopurine. Antimicrob Agents Chemother 1993;37:332–8.
[12] Robbins BL, Srinivas RV, Kim C, Bischofberger N, Fridland A. Anti-human immunodeficiency virus activity and cellular metabolism of a potential prodrug of the acyclic nucleoside phosphonate 9-R-(2-phosphonomethoxypropyl)adenine (PMPA), bis(isopropyloxymethylcarbonyl)-PMPA. Antimicrob Agents Chemother 1998;42:612–7.
[13] Naesens L, Bischofberger N, Augustijns P, Annaert P, Van den Mooter G, Arimilli MN, et al. Antiretroviral efficacy and pharmacokinetics of oral bis(isopropyloxycarbonyloxymethyl)-9-(2-phosphonylmethoxypropyl)adenine in mice. Antimicrob Agents Chemother 1998;42:1568–73.
[14] De Clercq E. From TIBO to rilpivirine: the chronicle of the discovery of the ideal nonnucleoside reverse transcriptase inhibitor. In: De Clercq E, editor, Antiviral drug strategies, Mannhold R, Kubinyi H, Folkers G editors, Methods and principles in medicinal chemistry. Weinheim, Germany: Wiley-VCH Verlag GmbH & Co.; 2011. p. 377–89.
[15] Ramanathan S, Mathias AA, German P, Kearney BP. Clinical pharmacokinetic and pharmacodynamic profile of the HIV integrase inhibitor elvitegravir. Clin Pharmacokinet 2011;50:229–44.
[16] Xu L, Liu H, Murray BP, Callebaut C, Lee MS, Hong A, et al. Cobicistat (GS-9350): a potent and selective inhibitor of human CYP3A as a novel pharmacoenhancer. ACS Med Chem Lett 2010;1:209–13.
[17] Tsai CC, Emau P, Follis KE, Beck TW, Benveniste RE, Bischofberger N, et al. Effectiveness of postinoculation (R)-9-(2-phosphonylmethoxypropyl) adenine treatment for prevention of persistent simian immunodeficiency virus SIVmne infection depends critically on timing of initiation and duration of treatment. J Virol 1998;72:4265–73.
[18] Otten RA, Smith DK, Adams DR, Pullium JK, Jackson E, Kim CN, et al. Efficacy of postexposure prophylaxis after intravaginal exposure of pig-tailed macaques to a human-derived retrovirus (human immunodeficiency virus type 2). J Virol 2000;74(20):9771–5.
[19] Van Rompay KK, McChesney MB, Aguirre NL, Schmidt KA, Bischofberger N, Marthas ML. Two low doses of tenofovir protect newborn macaques against oral simian immunodeficiency virus infection. J Infect Dis 2001;184:429–38.
[20] Van Rompay KK, Miller MD, Marthas ML, Margot NA, Dailey PJ, Canfield DR, et al. Prophylactic and therapeutic benefits of short-term 9-[2-(R)-(phosphonomethoxy)propyl]adenine (PMPA) administration to newborn macaques following oral inoculation with simian immunodeficiency virus with reduced susceptibility to PMPA. J Virol 2000;74:1767–74.
[21] Subbarao S, Otten RA, Ramos A, Kim C, Jackson E, Monsour M, et al. Chemoprophylaxis with tenofovir disoproxil fumarate provided partial protection against infection with simian human immunodeficiency virus in macaques given multiple virus challenges. J Infect Dis 2006;194:904–11.
[22] Parikh UM, Dobard C, Sharma S, Cong ME, Jia H, Martin A, et al. Complete protection from repeated vaginal simian–human immunodeficiency virus exposures in macaques by a topical gel containing tenofovir alone or with emtricitabine. J Virol 2009;83:10358–65.
[23] Grant RM, Buchbinder S, Cates Jr W, Clarke E, Coates T, Cohen MS, et al. AIDS. Promote HIV chemoprophylaxis research, don't prevent it. Science 2005;309:2170–1.
[24] Youle M, Wainberg MA. Could chemoprophylaxis be used as an HIV prevention strategy while we wait for an effective vaccine? AIDS 2003;17:937–8.
[25] Page-Shafer K, Saphonn V, Sun LP, Vun MC, Cooper DA, Kaldor JM. HIV prevention research in a resource-limited setting: the experience of planning a trial in Cambodia. Lancet 2005;366:1499–503.
[26] Singh JA, Mills EJ. The abandoned trials of pre-exposure prophylaxis for HIV: what went wrong? PLoS Med 2005;2:e234.
[27] Lange JM. We must not let protestors derail trials of pre-exposure prophylaxis for HIV. PLoS Med 2005;2:e248.
[28] Vissers DC, Voeten HA, Nagelkerke NJ, Habbema JD, de Vlas SJ. The impact of pre-exposure prophylaxis (PrEP) on HIV epidemics in Africa and India: a simulation study. PLoS One 2008;3:e2077.
[29] Liu AY, Grant RM, Buchbinder SP. Preexposure prophylaxis for HIV: unproven promise and potential pitfalls. JAMA 2006;296:863–5.
[30] Cardo DM, Culver DH, Ciesielski CA, Srivastava PU, Marcus R, Abiteboul D, et al. A case–control study of HIV seroconversion in health care workers after percutaneous exposure Centers for Disease Control and Prevention Needlestick Surveillance Group. N Engl J Med 1997;337:1485–90.
[31] Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, et al. Reduction of maternal–infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med 1994;331:1173–80.
[32] Rohan LC, Moncla BJ, Kunjara Na Ayudhya RP, Cost M, Huang Y, Gai F, et al. In vitro and ex vivo testing of tenofovir shows it is effective as an HIV-1 microbicide. PLoS One 2010;5:e9310.
[33] Abdool Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science 2010;329:1168–74.
[34] Peterson L, Taylor D, Roddy R, Belai G, Phillips P, Nanda K, et al. Tenofovir disoproxil fumarate for prevention of HIV infection in women: a phase 2, double-blind, randomized, placebo-controlled trial. PLoS Clin Trials 2007;2:e27.
[35] Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med 2010;363:2587–99.
[36] IAS 2011: final iPrEX analysis confirms PrEP effectiveness for gay men; 29 July 2011. http://www.hivandhepatitis.com/hiv-prevention/hiv-prep/3113-ias-2011-final-iprex-analysis-confirms-prep-effectiveness.
[37] Grant R, McMahan V, Liu A, Guanira J, Casapia M, Lama J, et al. Completed observation of the randomized placebo-controlled phase of iPrEx: daily oral FTC/TDF pre-exposure HIV prophylaxis among men and trans women who have sex with men. In: 6th international AIDS society conference on HIV pathogenesis, treatment and prevention (IAS 2011); 2011. Abstract WELBC04.
[38] Liu A, Huang Y, Defechereux P, McMahan V, Eden C, Guanira J, et al. Hair as a biological marker of daily oral pre-exposure prophylaxis (PrEP) adherence and tenofovir/emtricitabine (TFV/FTC) exposure in the Global iPrEx Study. In: 6th international AIDS society conference on HIV pathogenesis, treatment and prevention (IAS 2011); 2011. Abstract MOLBPE037.
[39] Gilmore H, Liu A, Amico KR, McMahan V, Goicochea P, Vargas L, et al. Adherence/drug detection rates and study participant experiences of counseling support among MSM in the iPrEx pre-exposure prophylaxis (PrEP) trial in San

Francisco, United States. In: 6th international AIDS society conference on HIV pathogenesis, treatment and prevention (IAS 2011); 2011. Abstract TUPE363.
[40] Abdool Karim SS, Baxter C. Antiretroviral prophylaxis for the prevention of HIV infection: future implementation challenges. HIV Ther 2009;3:3–6.
[41] Willyard C. A preemptive strike against HIV. Nat Med 2009;15:126–9.
[42] van Griensven F, Thienkrua W, Sukwicha W, Wimonsate W, Chaikummao S, Varangrat A, et al. Sex frequency and sex planning among men who have sex with men in Bangkok Thailand: implications for pre- and post-exposure prophylaxis against HIV infection. J Int AIDS Soc 2010;13:13.
[43] García-Lerma JG, Otten RA, Qari SH, Jackson E, Cong ME, Masciotra S, et al. Prevention of rectal SHIV transmission in macaques by daily or intermittent prophylaxis with emtricitabine and tenofovir. PLoS Med 2008;5:e28.
[44] García-Lerma JG, Cong ME, Mitchell J, Youngpairoj AS, Zheng Q, Masciotra S, et al. Intermittent prophylaxis with oral Truvada protects macaques from rectal SHIV infection. Sci Transl Med 2010;2(14). ra4.
[45] Microbicide Trials Network. MTN-003. http://www.mtnstopshiv.org/about/hiv_aids.
[46] CDC trial and another major study find PrEP can reduce risk of HIV infection among heterosexuals; July 13, 2011. http://www.cdc.gov/media/archives.htm.
[47] University of Washington. Partners PrEP Study. Pivotal study finds that HIV medications are highly effective as prophylaxis against HIV infection in men and women in Africa; July 13, 2011. http://depts.washington.edu/uwicrc/research/studies/PrEP.html.
[48] Two studies show pills can prevent HIV infection; July 13, 2011. http://www.nytimes.com/2011/07/14/health/research/14aids.html.
[49] De Clercq E. Anti-HIV drugs: 25 compounds approved within 25 years after the discovery of HIV. Int J Antimicrob Agents 2009;33:307–20.
[50] De Clercq E, Holý A. Acyclic nucleoside phosphonates: a key class of antiviral drugs. Nat Rev Drug Discov 2005;4:928–40.
[51] De Clercq E. The clinical potential of the acyclic (and cyclic) nucleoside phosphonates: the magic of the phosphonate bond. Biochem Pharmacol 2011;82:99–109.