| ***Study name*****Author, year** | **Interventions** | **Clinical health outcomes** | **Adverse events** | **Resistance** |
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| *ADAPT/ HPTN 067*Bekker 2018122 | A. Daily TDF-FTC (n=59)B. Time-driven TDF-FTC (one tablet twice a week, plus a dose after sex; n=59)C. Event-driven TDF-FTC (one tablet both before and after sex; n=60) | A vs. B vs. CHIV infection: 0% (0/59) vs. 3% (2/59) vs. 3% (2/60); A vs. B: RR, 0.20 (95% CI, 0.01 to 4.08); A vs. C: RR, 0.20 (95% CI, 0.01 to 4.15) | A vs. B vs. CAny headache, dizziness, or lightheadedness: 12% (43/348) vs. 6% (20/331) vs. 8% (26/332); A vs. B: OR, 2.19 (95% CI, 1.13 to 4.27); A vs. C: OR, 1.66 (95% CI, 0.88 to 3.13)Any GI symptom: 11% (37/348) vs. 9% (29/331) vs. 5% (18/332); A vs. B: OR, 1.24 (95% CI, 0.61 to 2.51); A vs. C: OR, 2.08 (95% CI, 0.98 to 4.40) | One participant in the time-driven group who seroconverted had M184Ile and L65Arg resistance |
| *ADAPT/ HPTN 067* Grant, 2018123 | A. Daily TDF-FTC (n=119)B. Time-driven TDF-FTC (one tablet twice a week, plus a dose after sex e; n=119)C. Event-driven TDF-FTC (one tablet both before and after sex; n=119) | A vs. B vs. CHIV infection: 0.8% (1/119) vs. 0% (0/119) vs. 0% (0/119); A vs. B; A vs. C: RR, 3.03 (95% CI, 0.12 to 75) South Africa (from Bekker 2017), Bangkok and Harlem sites combined: 0.6% (1/178) vs. 1.1% (2/178) vs. 1.1% (2/179); A vs. B: RR, 0.50 (95% CI, 0.04 to 5.53); A vs. C: RR, 1.01 (95% CI, 0.14 to 7.22) | A vs. B vs. CBangkokProportion of visits when patients reported neurologic events: 14.2% vs. 14.3% vs. 13.3% Proportion of visits when patients reported GI events: 13.1% vs. 8.5% vs. 10.5%HarlemProportion of visits when patients reported neurologic events: 6.1% vs. 3.3% vs. 4.5%Proportion of visits when patients reported GI events: 8.0% vs. 5.8% vs. 7.1% | No resistance in the Bangkok or Harlem cohorts |
| *Bangkok Tenofovir Study* Choopanya, 201397\* and Martin, 2015109 | A. Tenofovir 300mg once daily (n=1,204)B. Placebo (n=1,209)Participants could choose directly observed therapy or monthly take-home prescriptions, and switch at monthly followup appointments | A vs. BHIV infection: 1.4% (17/1,204) vs. 2.6% (33/1,207); RR, 0.52 (95% CI, 0.29 to 0.92) | A vs. BDeaths: 4.1% (49/1,204) vs. 4.8% (58/1,209); RR, 0.85 (95% CI, 0.58 to 1.23)Serious adverse events: 19% (227/1,204) vs. 20% (246/1,209); RR, 0.93 (95% CI, 0.79 to 1.09)Grade 4 adverse events: 2% (28/1,204) vs. 3% (31/1,209)Grade 3 adverse events: 12% (147/1,204) vs. 12% (142/1,209)Fracture/broken bone: 7.8% (94/1,204) vs. 6.0% (73/1,209); RR, 1.29 (95% CI, 0.96 to 1.74)Nausea and vomiting: 7.8% (96/1,204) vs. 4.9% (59/1,209); RR, 1.63 (95% CI, 1.19 to 2.24)Renal disease: 1% (13/1,204) vs. 1% (11/1,209); RR, 1.19 (95% CI, 0.53 to 2.64) | No tenofovir resistance mutations (K65R, K70E) in either group |
| *Bangkok Tenofovir Study* Martin, 2014108 | Same as Choopanya 2013 | Same as Choopanya 2013 | A vs. BCreatinine, grade 1 (increase ≥0.5 mg/dL from baseline): 3.1% (37/1,204) vs. 2.3% (28/1,209); p=0.27Creatinine, grade 2 (2.1 to 3.0 mg/dL): 0.2% (2/1,204) vs. 0% (0/1,209); p=0.25 Creatinine, grade 3 to 4 (≥3.1 mg/dL): 0.3% (3/1,204) vs. 0.3% (3/1,209); p=0.99 Creatinine clearance (Cockcroft-Gault) rate <50 mL/min: 3.7% (45/1,204) vs. 2.2% (26/1,209); p=0.01Acute renal failure: 0.08% (1/1,204) vs. 0.08% (1/1,209)All 7 participants with grade 2, 3, and 4 creatinine results permanently stopped taking the study drug and serum creatinine levels returned to normal in all except 1 in the tenofovir group who was diagnosed with diabetes and hypertension during the studyA (n=524) vs. B (n=511)Mean creatinine clearance, month 60Cockcroft-Gault method: 91.8 vs. 97.0 mL/min; p=0.002GFR (Modification of Diet in Renal Disease method): 88.5 vs. 91.9 mL/min/1.73 m2; p=0.003GFR (Chronic Kidney Disease Epidemiology Collaboration method): 97.4 vs. 100.7 mL/min/1.73 m2; p=0.002A vs. BLongitudinal analysis through month 60Cockcroft-Gault method: slope -0.04, p<0.001 vs. slope 0.02, p=0.08; between-group p<0.001GFR (Modification of Diet in Renal Disease method): slope -0.04, p<0.001 vs. slope -0.02, p=0.004; between-group p=0.12GFR (Chronic Kidney Disease Epidemiology Collaboration method): slope -0.06, p<0.01 vs. slope -0.04, p<0.001; between-group p=0.07 | Same as Choopanya 2013 |
| *FEM-PrEP*Van Damme, 2012120\* and Agot, 201595 | A. Oral TDF-FTC 300/200 mg once daily (n=1,062) B. Placebo, once daily (n=1,058) | A vs. B HIV infection: 5% (31/1,024) vs. 5% (35/1,032); HR, 0.94 (95% CI, 0.59 to 1.52); NNT, 275Risk behaviors: Narratively described reduction in number of partners, vaginal sex acts, and sex without a condom from baseline, no between-group data reported | A vs. BMortality: 0.1% (1/1,024) vs. 0.1% (1/1,032); RR, 1.01 (95% CI, 0.06 to 16)Any serious adverse event: 3.2% (33/1,025) vs. 2.2% (23/1,033); RR, 1.43 (95% CI, 0.84 to 2.42)Any adverse event: 74.1% (760/1,025) vs. 72.3% (747/1,033); RR, 1.01 (95% CI, 0.93 to 1.09)Withdrawals due to adverse event: 5.3% (55/1,025) vs. 3.2% (33/1,033)Withdrawals due to hepatic or renal lab abnormalities (temporary or permanent): 4.7% (48/1,024) vs. 3.0% (31/1,032)Elevated ALT (>Grade 3): 0.6% (6/1,025) vs. 0.8% (8/1,033); RR, 0.75 (95% CI, 0.26 to 2.17)Elevated AST (>Grade 3): 0.3% (3/1,025) vs. 0.1% (1/1,033); RR, 3.01 (95% CI, 0.31 to 28.9)Elevated creatinine (>Grade 2): 0.4% (4/1,025) vs. 0.2% (2/1,033); RR, 2.01 (95% CI, 0.36 to 10.95)Withdrawals due to renal events: 0.1% (1/1,025) vs. 0% (0/1,033) Trichomoniasis: 3.5% (36/1,024) vs. 5.8% (60/1,032); RR, 0.60 (95% CI, 0.40 to 0.91)Candidiasis: 15.2% (156/1,024) vs. 15.2% (157/1,032); RR, 1.00 (95% CI, 0.82 to 1.23)Gonorrhea: 4.9% (50/1,024) vs. 3.2% (33/1,032); RR, 1.53 (95% CI, 0.99 to 2.35)Chlamydia: 13.3% (136/1,024) vs. 12.0% (124/1,032); RR, 1.11 (95% CI, 0.88 to 1.39)Nausea: 4.9% (50/1,024) vs. 3.1% (32/1,032); RR, 1.57 (95% CI, 1.02 to 2.43)Vomiting: 3.6% (37/1,024) vs. 1.2% (12/1,032); RR, 3.11 (95% CI, 1.63 to 5.92)Diarrhea: 1.7% (17/1,024) vs. 0.8% (8/1,032); RR, 2.14 (95% CI, 0.93 to 4.94)Serious GI events: 0.4% (4/1,025) vs. 0.1% (1/1,033) Withdrawals due to GI adverse events: 0.1% (1/1,025) vs. 0% (0/1,033)Any adverse pregnancy-related outcomes, among women who became pregnant: 32.4% (24/74) vs. 23.5% (12/51); RR, 1.38 (95% CI, 0.76 to 2.50)Spontaneous abortion, among women who became pregnant: 14.9% (11/74) vs. 13.7% (7/51); RR, 1.08 (95% CI, 0.45 to 2.61) | A vs. BHIV-uninfected at time of enrollment K65R mutation: 0% vs. 0%K70E mutation: 0% vs. 0%M184V mutation: 75% (3/4) vs. 100% (1/1) M184I mutation: 25% (1/4) vs. 0% |
| *FEM-PrEP*Mandala, 2014106 | Same as Van Damme 2012 | NR | Elevated creatinine (Grade 1+): 0.08 vs. 0.67 (estimated from figure), cumulative probability p=0.128Elevated creatininemia (Grade 2+): 0.4% (4/1,025) vs. 0.2% (2/1,033); all cases resolved or decreased to grade 1 by 28 weeks following drug withdrawal Elevated phosphatemia (Grade 2+): 0.23 vs. 0.22 (estimated from figure), cumulative probability p=0.621Elevated ALT (Grade 1+): higher in TDF-FTC group, cumulative probability p=0.025 Elevated AST (Grade 1+): higher in TDF-FTC group, cumulative probability p=0.025 Elevated ALT and/or AST (Grade 3+): 0.78% (8/1,025) vs. 0.77% (8/1,033) | Same as Van Damme 2012 |
| Grohskopf, 201385\* (CDCSafety Study) | A. TDF, 300 mg orally daily, immediately or after a 9-month delay (n=201)B. Placebo, immediately or after a 9 month delay (n=199) | A vs. BHIV infection: 0% (0/201) vs. 3.5% (7/199); RR 0.07 (95% CI, 0.004 to 1.15); NNT 29 | A vs. BDeath: 0.5% (1/201) vs. 0% (0/199); RR, 2.97 (95% CI, 0.12 to 72.5)Serious adverse events: 5% (10/201) vs. 4% (8/199); RR, 1.24 (95% CI, 0.50 to 3.07)Fracture: 5.5% (15/201) vs. 1.9% (5/199); RR, 1.92 (95% CI, 0.49 to 7.5)Loss of bone density: 6.3% (9/201) vs. 3.7% (5/199); RR, 1.72 (95% CI, 0.6 to 4.98)Grade 3 or 4 adverse events: 17.9% (36/201) vs. 13.1% (26/199)Nausea: 13.4% (27/201) vs. 6.5% (13/199); RR, 2.06 (95% CI, 1.09 to 3.87)Diarrhea: 20.9% (42/201) vs. 28.6% (57/199); RR, 0.73 (95% CI, 0.52 to 1.03)Elevated serum creatinine: 1% (2/201) vs. 3% (6/199); RR, 0.33 (95% CI, 0.07 to 1.62)Withdrawal due to creatinine abnormality: 0% (0/201) vs. 1% (2/199)Fracture data from Food and Drug Administration: 9 vs. 5 | No K65R mutations were noted among any seroconverting participants (n=7; 3 TDF, 4 placebo) |
| Liu, 2011104(companion to Grohskopf, 2013) | Same as Grohskopf 2013 | NR | A vs. BFracture: 6.4% (6/94) vs. 4.4% (4/90); p=0.75BMD femoral neck: 1.1% mean net decrease in TDF group vs. placebo (95% CI, 0.4 to 1.9; p=0.004)BMD total hip: 0.8% mean net decrease in TDF group vs. placebo (95% CI, 0.3 to 1.3; p=0.003)BMD L2-L4 spine: 0.7% mean net decrease in TDF group vs. placebo (95% CI, -0.1 to 1.5; p=0.11)After adjustment for those taken off study drug due to >5% drop in BMD or low BMD:BMD femoral neck: 1.2% mean net decrease in TDF group vs. placebo (p=0.002) BMD total hip: 0.8% mean net decrease in TDF group vs. placebo (p=0.003) BMD L2-L4 spine: 0.9% mean net decrease in TDF group vs. placebo (p=0.039)A vs. B, % change >3% loss in BMD from baseline at: Femoral neck: 36% vs. 20%; p=0.02Total hip: 14% vs. 3%; p=0.02L2-L4 spine: 17% vs. 15%; p=0.69 | Same as Grohskoph 2013 |
| *IAVI Kenya Study* Mutua, 201253 | A. Daily TDF-FTC 300/200 mg (n=24)B. Intermittent (Monday, Friday and within 2 hours postcoital, not to exceed 1 dose/day) TDF-FTC (n=24)C. Daily placebo (n=12)D. Intermittent placebo (n=12) | A vs. B vs. C vs. DHIV infection: Narrative report of one HIV infection in a placebo group participant (daily or intermittent NR) HIV immune response:Positive IFN-y, week 16: 0 vs. 1 vs. 0 vs. 0Positive Env peptide: 0 vs. 2 vs. 0 vs. 0Positive RT peptide: 0 vs. 0 vs. 0 vs. 1Risk behavior, number of sexual partners: No between-group data reported; narrative report of increase from median 3 to 4 partners at month 4 | A vs. B vs. C vs. DSevere or very severe adverse event: 13% (3/24) vs. 4% (1/24) vs. 0% vs. 0% Any GI adverse event, A + B vs. C + D: 20/48 (42%) vs. 21% (5/24) Elevated serum creatinine, A + B vs. C + D: 6% (3/48) vs. 0% (0/24) Abnormal creatinine clearance: 2% (1/48) vs. 4% (1/24) | NR |
| *IAVI Uganda Study* Kibengo, 201354 | A. Daily TDF-FTC 300/200 mg (n=24)B. Intermittent (Monday, Friday and within 2 hours postcoital, not to exceed 1 dose/day) TDF-FTC 300/200 mg (n=24)C. Daily placebo (n=12)D. Intermittent placebo (n=12) | A vs. B vs. C vs. DHIV infection: Narrative report of no infections in any groupA + B vs. C + DPregnancy outcomes: 1 spontaneous abortion and 1 molar pregnancy vs. 1 term pregnancyHIV immune response: Positive Env response, week 16: 1 vs. 0 vs. 1 vs. 0 (no other data reported)Positive IFN-y ELISPOT, week 16: 0 vs. 1 vs. 0 vs. 0 (no other data reported)Risk behavior, number of sexual partners: Reported to be 1 (IQR, 1 to 1) for all groups | A vs. B vs. C vs. DSevere or very severe adverse event: 0% (0/24) vs. 0% (0/24) vs. 0% (0/12) vs. 8% (1/12) Severe neutropenia, A + B vs. C + D: 0% (0/48) vs. 4.1% (1/24) GI complaint, A + B vs. C + D: 33% (16/48) vs. 29% (7/24) Elevated serum creatinine, A + B vs. C + D: 4% (2/48) vs. 0% (0/24)Spontaneous abortion, among women who became pregnant, A + B vs. C + D: 100% (1/1) vs. 0% (0/1) | NR |
| *IPERGAY*Molina, 201552 | A. On demand TDF-FTC 300/200 mg (n=199)B. Placebo (n=201) On demand dosing schedule: 1. Two pills 2 to 24 hours before sex; third pill 24 hours after first drug intake; fourth pill 24 hours laterIn the case of multiple consecutive episodes of sexual intercourse, participants were instructed to take one pill per day until the last sexual intercourse, then take two postexposure pills. When resuming pre-exposure prophylaxis, participants were instructed to take a loading dose of two pills unless the last drug intake was less than 1 week earlier, in which case they were instructed to take only one pill. | A vs. BHIV infection: 2 (0.91/100 person-years) vs. 14 (6.6/100 person years); RR, 0.14 (95% CI, 0.03 to 0.63); NNT, 17; no resistance or mutations reportedNumber of sexual partners within past 2 months: 7.5 vs. 8; p=0.001Any newly acquired STI: 41% vs. 33%No difference in total number of sexual episodes in previous 4 weeks (p=0.07), or proportion of receptive anal intercourse episodes without condoms (p=0.07) or any anal intercourse without condoms (p=0.90) | A vs. BMortality: No deaths in either groupSerious adverse events: 10% (20/199) vs. 8% (17/201); RR, 1.19 (95% CI, 0.64 to 2.20)Any grade 3 or 4 event: 10% (19/199) vs. 7.5% (15/201); RR, 1.28 (95% CI, 0.67 to 2.45)Withdrawals due to adverse event: 0.5% (1/199) vs. 0% (0/201); RR, 3.03 (95% CI, 0.12 to 74)Fracture: 1.5% (3/199) vs. 3.0% (6/201); RR, 0.51 (95% CI, 0.44 to 2.47)Any plasma creatinine elevation: 18% (35/199) vs. 10% (20/201)Grade 2 plasma creatinine elevation: 0% (0/199) vs. 0.5% (1/201); RR, 0.34 (95% CI, 0.01 to 8.22)Proteinuria ≥2+: 5.5% (11/199) vs. 4.5% (9/201); RR, 1.23 (95% CI, 0.52 to 2.91)Glycosuria ≥2+: 0.5% (1/199) vs. 0% (0/201); RR, 3.03 (95% CI, 0.12 to 74)Grade 4 ALT elevation: 0.5% (1/199) vs. 1.5% (3/201); RR, 1.08 (95% CI, 0.38 to 3.01)Any GI adverse event: 14% (28/199) vs. 5.0% (10/201)Nausea: 8.0% (16/199) vs. 1.0% (2/201); RR, 8.08 (95% CI, 1.88 to 35)Diarrhea: 4.0% (8/199) vs. 3.0% (6/201); RR, 1.35 (95% CI, 0.48 to 3.81)No serious renal or GI adverse events in either groupHCV infection: 1.5% (3/199) vs. 2.5% (5/201) | None of the participants who acquired HIV infection after enrollment (n=16) had resistance mutations; mutations in 3 participants with HIV infection at time of enrollment NR |
| *iPrEx*Grant, 2010100\* | A. TDF-FTC 300/200 mg (n=1,251)B. Placebo (n=1,248) | A vs. BHIV infection: 3.0% (38/1,251) vs 5.8% (72/1,248); HR, 0.53 (95% CI, 0.36 to 0.78); NNT, 37 | A vs. BDeath: 0.1% (1/1,251) vs. 0.3% (4/1,248); RR, 0.25 (95% CI, 0.03 to 2.23)Serious adverse events: 5% (60/1,251) vs. 5% (67/1,248); RR, 0.89 (95% CI, 0.64 to 1.25)Withdrawal due to adverse event: 6.3% (79/1,251) vs 5.8% (72/1,248)Acute HBV infection: 0.1% (2/1,244) vs. 0.0% (1/1,217); RR, 1.96 (95% CI, 0.18 to 21.6)Syphilis: 4.2% (527/1,244) vs. 4.0% (491/1,217); OR, 0.54 (95% CI, 0.35 to 0.81)Warts: 9.8% (122/1,244) vs. 9.0% (110/1,217); OR, 1.09 (95% CI, 0.83 to 1.43)Urethral gonorrhea: 1.1% (14/1,244) vs. 1.4% (17/1,217); OR, 0.80 (95% CI, 0.39 to 1.64)Urethral chlamydia: 0.8% (10/1,244) vs. 1.2% (14/1,217); OR, 0.70 (95% CI, 0.31 to 1.57)Bone fracture: 1% (15/1,251) vs. 1% (11/1,248); RR, 1.36 (95% CI, 0.63 to 2.95)Diarrhea: 3.7% (46/1,251) vs. 4.5% (56/1,248); RR, 0.82 (95% CI, 0.56 to 1.20)Grade 3 or 4 diarrhea: (3/1,251) vs. (2/1,248)Nausea: 1.6% (20/1,251) vs. 0.7% (9/1,248); RR, 2.21 (95% CI, 1.01 to 4.85)Grade 3 or 4 nausea: No cases in either groupPermanent discontinuation of study drug: 2% (25/1,251) vs. 2% (27/1,248); RR, 0.92 (95% CI, 0.54 to 1.58)Permanent or temporary discontinuation of study drug: 6% (79/1,251) vs. 6% (72/1,248); RR, 1.09 (95% CI, 0.80 to 1.49)HSV-2: 9.7% (65/671) vs 8.9% (60/676); RR, 1.12 (95% CI, 0.80 to 1.56)Fracture data from Food and Drug Administration: 21 vs. 17 | 3 cases of resistance (2 TDF-FTC, 1 placebo); all had detectable plasma HIV RNA at time of enrollment:TDF-FTC case 1: M184V mutation (timing of resistance: secondary) TDF-FTC case 2: M184I mutation (timing of resistance: indeterminate)Placebo case 1: M184V, T215Y, and K103N mutations (timing of resistance: primary) |
| *iPrEx* Deutsch, 201598 | Transgender women onlyA. TDF-FTC 300/200 mg (n=170)B. Placebo (n=169) | Same as Grant 2010 | A vs. BDeath: 0.6% (1/170) vs. 0.6% (1/169); OR, 0.99 (95% CI, 0.06 to 16)Moderate/severe adverse events: 18% (31/170) vs. 17% (28/169); OR, 1.12 (95% CI, 0.64 to 2.97)Liver function abnormalities: 4% (6/170) vs. 3% (5/169); OR, 1.20 (95% CI, 0.36 to 4.01) | Same as Grant 2010 |
| *iPrEx*Liu, 2014105 | Same as Grant 2010 | Same as Grant 2010 | Same as Grant 2010 | Same as Grant 2010 |
| *iPrEx*Marcus, 2014107 | *HSV-2 negative substudy only*A. TDF-FTC 300/200 mg (n=692)B. Placebo (n=691) | Same as Grant 2010 | A vs. BHSV infection: 9.7% (65/671) vs. 8.9% (60/676); OR, 1.09 (95% CI, 0.75 to 1.58)HSV ulcer adverse event grade ≥2: 2.9% vs. 65.9%; p<0.05Perianal ulcer on STI exam: 4% vs. 5%; p=NSGroin ulcer on STI exam: 3% vs. 2%; p=NS | Same as Grant 2010 |
| *iPrEx* Mulligan, 2015114 | *BMD substudy only*A. TDF-FTC 300/200 mg (n=247)B. Placebo (n=251) | Same as Grant 2010 | A vs. BSpine BMD, mean difference at treatment discontinuation: -0.84 (95% CI, -1.51 to -0.16)Hip BMD, mean difference at treatment discontinuation: -0.74 (95% CI, -1.19 to -0.29)Spine BMD, mean difference at poststop: -0.45 (95% CI, -1.30 to 0.30)Hip BMD, mean difference at poststop: -0.76 (95% CI, -1.39 to -0.13)Fracture, DEXA substudy only (see also Grant 2010, above): No participants who had fractures had BMD levels that met either ISCD criteria for low BMD or WHO criteria for osteoporosis at baseline or during the study | Same as Grant 2010 |
| *iPrEx* Solomon, 2014118 | Renal substudy onlyA. TDF-FTC 300/200 mg (n=563)B. Placebo (n=574) | Same as Grant 2010 | A vs. BPersistent creatinine elevation: 1% (7/563) vs. 0.2% (1/574); OR, 7.21 (95% CI, 0.88 to 59); all resolved by 20 weeks after PrEP withdrawalProximal tubulopathy, one indicator: 6% (34/563) vs. 5% (25/574); OR, 1.41 (95% CI, 0.83 to 2.40)Proximal tubulopathy, two indicators: 0% (0/563) vs. 0.3% (2/574); OR, 0.20 (95% CI, 0.01 to 4.24) | Same as Grant 2010 |
| *Partners PrEP*Baeten, 201270\* | A. Once-daily TDF 300 mg + placebo TDF-FTC (n=1,571)B. Once-daily TDF-FTC 300/200 mg + placebo TDF (n=1,565)C. Placebo TDF + placebo TDF-FTC (n=1,570)All participants received a comprehensive package of HIV-1 prevention services and were offered HBV vaccination | A vs. B vs. CHIV infection: 1.1% (17/1,572) vs. 0.8% (13/1,568) vs. 3.3% (52/1,586); A vs. B: RR, 1.30 (95% CI, 0.64 to 2.68) NNT, 397; A vs. C: RR, 0.33 (95% CI, 0.19 to 0.56)NNT, 46; B vs. C: RR, 0.25 (95% CI, 0.14 to 0.46) NNT, 41HIV infection among patients whose partner had not yet initiated ART: 14/17 vs. 13/13 vs. 50/52 | A vs. B. vs. CSerious adverse events: 7.4% (118/1,584) vs. 7.3% (115/1,579) vs. 7.4% (118/1,584)Death: 0.5% (8/1,584) vs. 0.5% (8/1,579) vs. 0.6% (9/1,584)Withdrawal due to adverse events: 0.6% vs. 0.7% vs. 0.6%Grade 4 adverse events: 2.1% (34/1,584) vs. 2.8% (44/1,579) vs. 2.5% (39/1,584)Grade 3 adverse events: 18.2% (289/1,584) vs. 18.6% (293/1,579) vs. 16.9% (268/1,584)Bone fracture: <1% (11/1,584) vs. 0.6% (9/1,579) vs. 0.8% (12/1,584) Elevated creatinine grade 1: 1.0% (16/1,584) vs. 1.1% (18/1,579) vs. 0.8%% (12/1,584)Elevated creatinine grade 2 or 3: 0.2% (3/1,584) vs. 0.1% (2/1,579) vs. 0.1% (1/1,584)Nausea: 0.2% (3/1,584) vs. 0.1% (1/1,579) vs. 0% (0/1,584); A vs. C: RR, 3.50 (95% CI, 0.18 to 68); B vs. C: RR, 1.51 (95% CI, 0.06 to 37)Diarrhea: 3.0% (48/1,584) vs. 2.4% (38/1,579) vs. 2.5% (39/1,584); A vs. C: RR, 1.23 (95% CI, 0.81 to 1.87); B vs. C: RR, 0.98 (95% CI, 0.63 to 1.52)STI (*N. gonorrhoeae, C. trachomatis,* or *T. vaginalis* ): 5.8% (102/1,584) vs. 4.2% (76/1,579) vs. 4.8% (85/1,584)Syphilis: 2% (28/1,584) vs. 2% (27/1,579) vs. 1% (23/1,584)Fracture data from Food and Drug Administration: 19 (PrEP) vs. 13 (placebo) | Total population A vs. B vs. CK65R mutation (TDF resistance): 5.0% (1/20) vs. 0% (0/15) vs. 0% (0/57)K70E mutation (TDF resistance): 0% (0/20) vs. 0% (0/15) vs. 0% (0/57)M184I mutation (FTC resistance): 0% (0/20) vs. 0% (0/15) vs. 0% (0/57)M184V mutation (FTC resistance): 0% (0/20) vs. 6.7% (1/15) vs. 0% (0/57)K65N mutation (TDF resistance): 5.0% (1/20) vs. 0% (0/15) vs. 0% (0/57)K70R mutation (TDF resistance): 5.0% (1/20) vs. 0% (0/15) vs. 0% (0/57)K103N or V106A mutations (NNRTI resistance): 10% (2/20) vs. 6.7% (1/15) vs. 1.8% (1/57)T215C mutation: 0% (0/20) vs. 0% (0/15) vs. 1.8% (1/57) HIV infected at time of enrollment A vs. B vs. CK65R mutation: 20% (1/5) vs. 0% (0/3) vs. 0% (0/6) K70E mutation: 0% (0/5) vs. 0% (0/3) vs. 0% (0/6) M184I mutation: 0% (0/5) vs. 0% (0/3) vs. 0% (0/6) M184V mutation: 0% (0/5) vs. 33.3% (1/3) vs. 0% (0/6) K70R mutation: 20% (1/5) vs. 0% (0/3) vs. 0% (0/6)K103N or V106A mutation: 0% (0/5) vs. 0% (0/3) vs. 0% (0/6) 25% (2/8) found to be infected at time of enrollment and randomized to PrEP developed resistance mutation (1 each K65R and M184V)HIV uninfected at time of enrollment A vs. B vs. C K65R mutation: 0% (0/15) vs. 0% (0/12) vs. 0% (0/51) K70E mutation: 0% (0/15) vs. 0% (0/12) vs. 0% (0/51) M184I mutation: 0% (0/15) vs. 0% (0/12) vs. 0% (0/51) M184V mutation: 0% (0/15) vs. 0% (0/12) vs. 0% (0/51) K70R mutation: 0% (0/15) vs. 0% (0/12) vs. 0% (0/51)K103N or V106A mutation: 13.3% (2/15) vs. 8.3% (1/12) vs. 2.0% (1/51) |
| *Partners PrEP*Celum 201480 | A. Once-daily TDF 300 mg + placebo TDF-FTC (n=528)B. Once-daily TDF-FTC 300/200 mg + placebo TDF (n=513) | Same as Baeten 2012 | A vs. B vs. CHSV-2 infection: 37/528 vs. 42/513 vs. 52/481; A vs. C: HR, 0.64 (95% CI, 0.42 to 0.98); RR, 0.65 (95% CI, 0.40 to 1.04); B vs. C: HR, 0.76 (95% CI, 0.51 to 1.14); RR, 0.76 (95% CI, 0.48 to 1.21)(A + B) vs. CHSV-2 infection: 79/1,041 vs. 52/481; HR, 0.70 (95% CI, 0.49 to 0.99); RR, 0.70 (95% CI, 0.50 to 0.98) | Same as Baeten 2012 |
| *Partners PrEP*Donnell, 201499 | Same as Baeten 2012 | Same as Baeten 2012 | Same as Baeten 2012 | Same as Baeten 2012 |
| *Partners PrEP*Haberer, 2013101 | Same as Baeten 2012 | NA | NA | NA |
| *Partners PrEP*Heffron, 2014102 | A. TDF or FTCB. Placebo | Same as Baeten 2012 | Same as Baeten 2012 | Same as Baeten 2012 |
| *Partners PrEP*Lehman, 2015103 | *Seroconverters only*A. Once-daily TDF 300 mg + placebo TDF-FTC (n=39)B. Once-daily TDF-FTC 300/200 mg + placebo TDF (n=25)C. Placebo TDF + placebo TDF-FTC (n=58) | Same as Baeten 2012 | Same as Baeten 2012 | A vs. B vs. C Total populationResistance frequencies >1%: 5.3% (2/38) vs. 20% (5/25) vs. 3.5% (2/58)HIV infected at time of enrollmentResistance frequencies >1%: 12.5% (1/8) vs. 50% (2/4) vs. 0% (0/6)HIV uninfected at time of enrollmentResistance frequencies >1%: 3.3% (1/30) vs. 14.3% (3/21) vs. 3.8% (2/52) |
| *Partners PrEP*Matthews, 2014110 | Oral TDF and TDF-FTC PrEP; placebo; risk reduction counseling, couples counseling, and condoms | Same as Baeten 2012 | Same as Baeten 2012 | Same as Baeten 2012 |
| *Partners PrEP*Mugo, 2014112 | *HIV-uninfected women only*A. Once daily TDF 300 mg (n=595)B. Once daily TDF-FTC 300/200 mg (n=565)C. Once daily placebo (n=621) | A vs. B vs. CPregnancy: 18.9% (112/595) vs. 14.1% (80/565) vs. 15.5% (96/621)Pregnancy loss: 27.7% (31/112) vs. 42.5% (34/80) vs. 32.3% (31/96); absolute difference for A vs. C, -4.6% (95% CI, -18.1% to 8.9%) and for B vs. C, 10.2% (95% CI, -5.3% to 25.7%)Preterm birth among live births: 2.5% (2/81) vs. 8.7% (4/46) vs. 7.7% (5/65); absolute difference for A vs. C, -5.2% (95% CI, -13.9% to 3.5%) and for B vs. C, 1.0% (95% CI, -11.3% to 13.3%)Any anomaly (among live births): 4.9% (4/81) vs. 8.5% (4/46) vs. 7.6% (5/65); absolute difference for A vs. C, -2.6% (95% CI, -12.0% to 6.7%) and for B vs. C, 0.9% (95% CI, -11.1% to 13.0%)Postpartum infant mortality: 1.2% (1/81) vs. 10.9% (5/46) vs. 6.1% (4/66); RR for A vs. C, 0.20 (95% CI, 0.02 to 1.8) and for B vs. C, 1.4 (95% CI, 0.38 to 5.4) Infant growth: No statistically significant differences in head circumference, length, or weight; some estimates indicated slightly faster growth in some measures for PrEP vs. placebo | Same as Baeten 2012 | Same as Baeten 2012 |
| *Partners PrEP*Mugwanya, 2015113 | A. Once daily TDF 300 mg (n=1,548)B. Once daily TDF-FTC 300/200 mg (n=1,545)C. Once daily placebo (n=1,547) | Same as Baeten 2012 | A vs. B vs. CeGFR mean difference (mL/min/1.73 m2): +0.14 vs. -0.22 vs. +1.37; difference for A vs. C, -1.23 (95% CI, -2.06 to -0.40) and for B vs. C, -1.59 (95% CI, -2.44 to -0.74)Serum GFR decline ≥25% from baseline (incidence/100 person-years): 1.8% vs. 2.5% vs. 2.2% by 36 months; adjusted HR for A vs. C, 1.33 (95% CI, 0.71 to 2.48) and for B vs. C, 1.45 (95% CI, 0.79 to 2.64)Elevated serum creatinine leading to study withdrawal: 0.1% (2/1,548) vs. 0.1% (2/1,545) vs. 0.1% (1/1,547) | Same as Baeten 2012 |
| *Partners PrEP*Murnane, 2013115 | Same as Baeten 2012 | Same as Baeten 2012 | Same as Baeten 2012 | Same as Baeten 2012 |
| *Partners PrEP*Murnane, 2015116 | Same as Baeten 2012 | Same as Baeten 2012 | Same as Baeten 2012 | Same as Baeten 2012 |
| *Partners PrEP*Were, 2014121 | *HIV-uninfected men only*A. Once-daily TDF 300 mg + placebo TDF- FTC (n=986)B. Once-daily TDF-FTC 300/200 mg + placebo TDF (n=1,013)C. Placebo TDF + placebo TDF-FTC (n=963) | A vs. B vs. CLive births: 152/192 vs. 162/193 vs. 146/198-Term birth: 142/192 vs. 148/193 vs. 135/198-Premature birth: 7/192 vs. 9/193 vs. 6/198 Pregnancy loss: 32/192 vs. 23/193 vs. 35/198-Loss at <20 weeks: 20/32 vs. 15/23 vs. 25/35-Loss at 20 to 36 weeks: 10/32 vs. 7/23 vs. 6/35-Loss at ≥37 weeks: 2/32 vs. 1/23 vs. 3/35 | NR | Same as Baeten 2012 |
| *Project PrEPare ATN 082*Hosek, 201394 | A. PrEP with daily TDF-FTC (n=20) + 3MV behavioral HIV prevention interventionB. Placebo (daily) + 3MV behavioral intervention (n=19) C. 3MV behavioral intervention, alone (n=19) | NR | A vs. B vs. CSerious adverse events: NoneNausea at 8 weeks: 24% vs 0% vs 6%ART resistance: NR | NR |
| *PROUD*McCormack, 201678 | A. Immediate PrEP with daily TDF-FTC 245/200 mg (n=275)B. Deferred PrEP for 1 year (n=269) | A vs. BHIV infection: 1.1% (3/268) vs. 7.5% (20/255); RR, 0.14(95% CI, 0.04 to 0.47); 1.2 cases/100 person-years (90% CI, 0.4 to 2.9) vs. 9.0/100 person-years (90% CI, 6.1 to 12.8); NNT, 13 | A vs. BMortality: 0.4% (1/275) vs. 0% (0/269)Serious adverse events: 8% (21/275) vs. 2% (6/269); RR, 3.42 (95% CI, 1.40 to 8.35)Fracture/broken bone: 1% (3/275) vs. 0.4% (1/269); RR, 2.93 (95% CI, 0.31 to 28)Diarrhea (serious): 1.5% (4/275) vs. 0% (0/269); RR, 8.80 (95% CI, 0.48 to 163)Vomiting (serious): 0.7% (2/275) vs. 0% (0/269); RR, 4.89 (95% CI, 0.24 to 101)Any STI: 57% (152/265) vs 50% (124/247); OR, 1.33 (95% CI, 0.94 to 1.89); aOR (adjusted for number of screenings for specific infection), 1.07 (95% CI, 0.78 to 1.46) Gonorrhea: 39% (103/261) vs. 37% (89/242); OR, 1.12 (95% CI, 0.78 to 1.61); aOR, 0.86 (95% CI, 0.62 to 1.20)Chlamydia: 30% (77/261) vs. 22% (54/242); OR, 1.46 (95% CI, 0.97 to 2.18); aOR, 1.27 (95% CI, 0.89 to 1.80)Syphilis: 11% (30/263) vs. 9% (22/247); OR, 1.32 (95% CI, 0.74 to 2.35); aOR, 1.29 (95% CI, 0.79 to 2.10)Rectal gonorrhoea or chlamydia: 36% (93/258) vs. 32% (77/238); OR, 1.18 (95% CI, 0.81 to 1.71); aOR, 1.00 (95% CI, 0.72 to 1.38)HCV infection: 1.2% (3/258) vs. 1.3% (3/238) | A vs. BAny HIV infectionM184I or M184V mutation: 40% (2/5) vs. not assessed K65R or K65E mutation: 0% (0/5) vs. not assessedHIV infected at time of enrollmentM184I or M184V mutation: 66.7% (2/3) vs. not assessedHIV uninfected at time of enrollmentM184I or M184V mutation: 0% (0/2) vs. not assessed |
| *Study of TDF* Peterson, 2007117 | A. TDF, 300 mg orally daily (n=469)1. B. Placebo (n=467)

All participants received HIV posttest counseling, and received condoms and risk reduction counseling at every monthly visit | A vs. BHIV infection: 0.5% (2/427) vs. 1.4% (6/432); RR, 0.34 (95% CI, 0.07 to 1.66); NNT, 109Condom use: increased from 52% to 95% at 1 year, no between-group data reported | A vs. BMortality: 0.2% (1/427) vs. 0.2% (1/432); RR, 1.01 (95% CI, 0.06 to 16)Serious adverse events: 2% (9/427) vs. 3% (13/432); RR, 0.70 (95% CI, 0.30 to 1.62)Abdominal pain: 5.6% (24/427) vs. 5.1% (22/432); RR, 1.10 (95% CI, 0.63 to 1.84)Malaria: 29.7% (127/427) vs. 31.0% (134/432); RR, 0.96 (95% CI, 0.78 to 1.17)Urinary tract infection: 5.4% (23/427) vs. 3.5% (15/432); RR, 1.55 (95% CI, 0.82 to 2.93)Vaginal candidiasis: 22.5% (96/427) vs. 22.0% (95/432); RR, 1.02 (95% CI, 0.80 to 1.31)No withdrawals due to AEs | Standard genotypic analysis revealed no evidence of drug resistance mutations |
| *TDF2*Thigpen, 2012119\* | A. Oral TDF-FTC 300/200 mg, once daily (n=611)B. Placebo, once daily (n=608) | A vs. BHIV infection: 1.6% (10/601) vs. 4.2% (26/606); RR, 0.39 (95% CI, 0.19 to 0.81); 1.2 cases/100 person-years (90% CI, 0.4 to 2.9) vs. 3.1 cases/100 person- years (90% CI, 0.03 to 3.2); NNT, 52 | A vs. BMortality: 0.3% (2/611) vs. 0.7% (4/608); RR, 0.50 (95% CI, 0.09 to 2.71)Serious adverse events: 10% (68/611) vs. 11% (79/608); RR, 0.85 (95% CI, 0.63 to 1.16)No Grade 3 or 4 creatinine elevation or GI events Fracture/broken bone: 1% (7/611) vs. 1% (6/608)Elevated creatinine: 0.2 (1/611) vs. 0% (0/608); RR, 2.98 (95% CI, 0.12 to 73.14)Diarrhea: 12.4% (76/611) vs. 10.7% (65/608)Nausea: 18.5% (113/611) vs. 7.1% (43/608)*Neisseria gonorrheae* infection: 4.6% (28/611) vs. 3.0% (18/608) *Chlamydia trachomatis* infection: 12.4% (76/611) vs. 12.3% (75/608) Trichomoniasis: 3.3% (20/611) vs. 3.0% (18/608)Genital herpes: 4.6% (28/611) vs. 5.8% (35/608)BMD changes, A (n=109) vs. B (n=112): There was a decline in T-scores and z-scores at the forearm, hip, and lumbar spine in participants who received TDF-FTC, compared with those who received placebo (p=0.004 for both T-scores and z-scores at the forearm and p<0.001 for both scores at the hip and lumbar spine)HSV-2: 4.6% (28/611) vs 5.8% (35/608); RR, 0.80 (95% CI, 0.49 to 1.29) | A vs. B0.2% (1/611; HIV RNA >750,000 copies/ML at enrollment. M184V, K65R, and A62V mutations) vs. 0.2% (1/608; HIV RNA <400 copies/mL at enrollment. K65R mutation) |
| *TDF2*Chirwa, 201496 | Same as Thigpen 2012 | Of 36 HIV infections, 33 occurred during the course of the study and 3 were retrospectively found to be acutely HIV infected at study entry; 9 occurred among those receiving TDF-FTC and 24 receiving placebo | Same as Thigpen 2012 | Of the 33 who acquired HIV during the course of the study, no resistance mutations were identified in their first RNA-positive samples or in any of their samples from subsequent study visits; 1 participant in the placebo group had low levels (<1%) of the K65R mutation, a level of expression attributable to replication error at and around codon 65 that has been observed with ART-naive HIV subtype C infections; 1 of the 3 participants who screened falsely negative at study entry and received TDF-FTC until HIV was diagnosed at month 7 developed the M184V mutation—this was retrospectively found to have occurred 1 month after study entry, and the A62V and K65R mutations occurred between 4 and 7 months after study entry; all mutations were at high levels |
| *VOICE*Marrazzo, 201576\* | A. Oral TDF 300 mg and TDF-FTC placebo (n=1,007)B. Oral TDF-FTC 300/200 mg and TDF placebo (n=1,003)C. Oral TDF placebo and oral TDF-FTC placebo (n=1,009)*Interventions outside the scope of this review:*D. Vaginal 1% TFV gel (n=1,007)E. Vaginal placebo gel (n=1,003)(all daily) | A vs. B vs. CNumber of HIV-1 infections: 5% (52/1,007) vs. 6% (61/1,003) vs. 6% (60/1,009); A vs. C: RR, 0.87 (95% CI, 0.61 to 1.25); B vs. C: RR, 1.02 (95% CI, 0.72 to 1.44)Effectiveness:TDF (group A): -49%; HR for infection, 1.49 (95% CI, 0.97 to 2.29)TDF-FTC (group B): -4.4%; HR for infection 1.04, (95% CI, 0.73 to 1.49)TFV gel (group D): 14.5%; HR for infection, 0.85 (95% CI, 0.61 to 1.21)HIV-1 incidence (cases per 100 person-years): 6.3 (95% CI, 4.7 to 8.3) vs. 4.7 (95% CI, 3.6 to 6.1) vs. 4.6 (95% CI, 3.5 to 5.9) vs. 6.0 (95% CI, 4.6 to 7.6) vs. 6.8 (95% CI, 5.3 to 8.6) | A vs. B vs. CMortality: 0% (0/1,007) vs. 0% (0/1,003) vs. 0.3% (3/1,009)Serious adverse events: 8.6% (87/1,007) vs. 12.2% (123/1,003) vs. 11.3% (114/1,009) Grade 4 events: 0.4% (4/1,007) vs. 1.4% (14/1,003) vs. 1.7% (17/1,009)Lower limb fracture: 0.2% (2/1,007) vs. 0.1% (1/1,003) vs. 0% (0/1,009) Creatinine event: 0.4% (4/1,007) vs. 1.3% (13/1,003) vs. 0.2% (2/1,009)Nausea grade 2 or higher: 1.3% (13/1,007) vs. 0.8% (8/1,003) vs. 1.5% (15/1,009)Vomiting grade 2 or higher: 0.1% (6/1,007) vs. 0.1% (6/1,003) vs. 0.1% (9/1,009)Diarrhea grade 2 or higher: 1.2% (12/1,007) vs. 1.8% (18/1,003) vs. 2.1% (21/1,009)Any Grade 3 or 4 GI event: 0% (0/1,007 vs. 0.3% (3/1,003) vs. 0.7% (7/1,009)Chlamydia infection: 10.4% (105/1,007) vs. 14.4% (144/1,003) vs. 15.2% (153/1,009)Gonococccal infection: 2.6% (26/1,007) vs. 4.6% (46/1,003) vs. 4.5% (45/1,009) Syphilis infection: 1.5% (15/1,007) vs. 1.0% (10/1,003) vs. 1.5% (15/1,009) | A vs. B vs. C Total populationK65R mutation (TDF resistance): 0% (0/70) vs. 0% (0/71) vs. 0% (0/69)K70E mutation (TDF resistance): 0% (0/70) vs. 0% (0/71) vs. 0% (0/69)M184V mutation (FTC resistance): 0% (0/70) vs. 4.2% (3/71) vs. 0% (0/69)M184I mutation (FTC resistance): 0% (0/70) vs. 1.4% (1/71) vs. 0% (0/69)HIV infected at time of enrollmentK65R mutation: 0% (0/5) vs. 0% (0/9) vs. 0% (0/1) K70E mutation: 0% (0/5) vs. 0% (0/9) vs. 0% (0/1) M184V mutation: 0% (0/5) vs. 22% (2/9) vs. 0% (0/1) M184I mutation: 0% (0.5) vs. 11% (1/9) vs. 0% (0/1)HIV uninfected at time of enrollmentK65R mutation: 0% (0/65) vs. 0% (0/62) vs. 0% (0/68) K70E mutation: 0% (0/65) vs. 0% (0/62) vs. 0% (0/68) M184V mutation: 0% (0/65) vs. 1.6% (1/62) vs. 0% (0/68) M184I mutation: 0% (0/65) vs. 0% (0/62) vs. 0% (0/68) |
| *VOICE*Mirembe, 2016111 | A. TDF (n=172)B. TDF-FTC (n=174)C. Placebo (n=172) | Same as Marrazzo 2015 | No significant differences were observed in the primary analysis comparing the mean percent changed in BMD TH and BMD LS from baseline to week 48 between the TDF or TDF-FTC arms compared with placebo; there was also no difference when the active arms were pooledA 3% decrease in BMD was observed in 24% and 17% participants for spine and hip, respectively, and did not differ significantly between active arms and placeboOutcomes after discontinuing active treatment for 68% (354/518) of participants: BMD increases at the spine and hip were observed after stopping study medication and were significantly greater in the active arm participants than placebo: 0.9% at the LS (p=0.007) and 0.7% at the TH (p=0.003); BMD at 48 weeks after active treatment discontinuation was at least as high as the mean BMD level at baseline | Same as Marrazzo 2015 |

\*Main study publication.

**Abbreviations**: 3MV=Many Men, Many Voices; ADAPT/HPTN=Alternative Dosing to Augment Pre-Exposure Prophylaxis Pill Taking/HIV Prevention Trials Network; ALT=alanine aminotransferase; aOR=adjusted odds ratio; ART=antiretroviral therapy; AST=aspartate aminotransferase; BMD=bone mineral density; CDC=Centers for Disease Control and Prevention; CI=confidence interval; DEXA=dual energy X-ray absorptiometry; eGFR=estimated glomerular filtration rate; ELISPOT=Enzyme-Linked ImmunoSpot assay; Env=Env peptide pool; FEM-PrEP=Pre-Exposure Prophylaxis Trial for HIV Prevention Among African Women; FTC=emtricitabine; GFR=glomerular filtration rate; GI=gastrointestinal; HBV=hepatitis B virus; HCV=hepatitis C virus; HR=hazard ratio; HSV=herpes simplex virus; IAVI=International AIDS Vaccine Initiative; IFN-y=interferon gamma; IPERGAY=Intervention Préventive de l’Exposition aux Risques Avec et Pour les GAYs; iPrEx=Pre-Exposure Prophylaxis Initiative; IQR=interquartile range; ISCD=International Society for Clinical Densiometry; L2=second lumbar vertebra; L4=fourth lumbar vertebra; LS=lumbosacral spine; NA=not applicable; NNRTI=nonnucleoside reverse transcriptase inhibitor; NNT=number needed to treat; NR=not reported; OR=odds ratio; PrEP=pre-exposure prophylaxis; PROUD=Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred; RNA=ribonucleic acid; RR=relative risk; RT=retention time; STI=sexually transmitted infection; TDF=tenofovir disoproxil fumarate; TDF2=Tenofovir Disoproxil Fumarate 2 Study; TFV=tenofovir; TH=thoracic vertebra; VOICE=Vaginal and Oral Interventions to Control the Epidemic; WHO=World Health Organization.