Appendix

Data from Phase 2 and Phase 3 Expanded Safety and Efficacy Clinical Trials

The presented data are referred to in Chapter 16, "Socioeconomic and Behavioral Factors Influencing Choice, Adherence and Success of Microbicide Formulations," and were compiled by its authors.

Table A.1 Cohorts and summary adherence data from Phase 2 and 3 expanded safety and efficacy clinical trials of microbicide candidates conducted between 1986 and 2013

Product (date)	Trial features	Trial outcomes	Adherence outcomes	Refs.
N-9 sponge (1986)	**Design and regimen:** RCT, cross-over, OL: N-9 sponge vs. control (nothing), sponge before 1st partner, after 3 partners, remove 6 h ALP. **Intended outcome:** NG/CT prevention. **Follow-up (retention rate):** 12 w, weekly FU, 6 w per arm. **Cohort (number, description):** 312 FSW, recruited from 4 massage parlors. **Sites:** 1 (Bangkok, Thailand). **Baseline characteristics:** A: μ 23 y; M: 40–42% single, 32–33% divorced; E: >50%, <7 y; NP: >50%, 5–10 PPW; FP: >95% HC (87–93% OC)	Sponge users partially protected against NG and CT, but increased risk of candidiasis	Not available (authors claim compliance was high due to unscheduled compliance checks; no specifics provided re-compliance rates or checks)	[1]

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Table A.1 (*Continued*)

Product (date)	Trial features	Trial outcomes	Adherence outcomes	Refs.
N-9 gel (1984–1986)	**Design and regimen:** Phase 3, RCT: N9 gel vs. PL (Koromex Crystal Clear Gel), pa. **Intended outcome:** NG/CT prevention [no info on SS calculation]. **Follow-up (retention rate):** 6 m, monthly FU (78% RET). **Cohort (number, description):** 818 ♀, 19–29 y, attending STD clinic. **Sites:** 1 (Birmingham, AL, USA). **Baseline characteristics:** A: μ 23 y; M: 18%; NP: μ 1 PPM during trial; CF: μ 5 APW during trial; FP: 75% OC	N-9 reduced NG/CT risk; stronger protective effect for ♀ using gel for majority of acts	Not available	[2]
N-9 film (1990)	**Design and regimen:** RCT, OL, partially blinded: N9 film vs. PL (lubricant), pa (clinicians blinded). **Intended outcome:** NG/CT prevention [no info on SS calculation]. **Follow-up (retention rate):** μ 3 w (1–9 w) FU (75% RET). **Cohort (number, description):** 343 ♀; recruited from 6 massage parlors where study procedures took place. **Sites:** 1 (Bangkok, Thailand). **Baseline characteristics:** A: 43–47% <20 y; M: 65–67% unmarried; E: 79–80% primary; NP: 44–46%, 8–14/w; Other: 64–66% ever had STD	N-9 reduced NG/CT rates by 25% overall and 40% in ♀ >75% compliant	24–32% ♀compliant for 0–50% of acts; 20–29% compliant for 51–75% of acts; 47–48% compliant for 76–100% of acts	[3]

N-9 sponge (1987–1990)	**Design and regimen:** Phase 3, RCT, OL: N-9 sponge v PL (suppository or gel), sponge before 1st partner, after 2–3 partners, remove 6 h ALP (PL qd). **Intended outcome:** 37 endpoints → 75% HIV risk reduction. **Follow-up (retention rate):** μ 9 m [1–46 m] (84% RET). **Cohort (number, description):** 138 FSW, 18 y+, enrolled through attendance at STD clinics. **Sites:** 1 (Nairobi, Kenya); estimated HIV incidence was 20%/y. **Baseline characteristics:** A: μ 29–30 y; CF: μ 42–56 APW; C: 51–54% of partners; FP: 22–28% OC	Study terminated early per DSMC recommendation due to AE	μ compliance: 81%, sponge, 90%, PL; 90% (sponge) and 95% (PL) users ≥50% compliant, 73% (sponge) and 90% (PL) users ≥75% compliant	[4]
N-9 suppository (1989–1990)	**Design and regimen:** Observational; Single arm, OL: N-9 + condom, pa. **Intended outcome:** HIV prevention [no info on SS calculation]. **Follow-up (retention rate):** 1 y, monthly FU, μ 8.1 m (92% RET). **Cohort (number, description):** 273 FSW, 18 y+, recruited from bars. **Sites:** 1 (Yaounde, Cameroon). **Baseline characteristics:** A: 73% ≤29 y; M: >90% single; E: 49% primary, 93% could read; B: 84% ≥1; NP: 64% ≥ 4–7 PPW; C: 58% never use; FP: none>15%	First epidemiological evidence that N-9 spermicides can reduce incidence of HIV infection (RCT needed)	20% ♀ reported no unprotected sex (neither N-9 or condom); 50% reported N-9 use >67% of acts; 50% reported condom use >63% of acts	[5] (see also [6])
N-9 suppository (1989–1990)	**Design and regimen:** Observational; Single arm, OL: N-9 + condom, pa. **Intended outcome:** NG prevention [no info on SS calculation]; secondary analysis from [5]. **Follow-up (retention rate):** 1 y, monthly FU, μ 8.1 m (92% RET). **Cohort (number,**	N-9 affords significant protection when condoms not used	μ 40% acts, N-9 + condom; μ 22% acts, N-9 alone; μ 25% acts, condom alone; μ 12% acts, neither; 8% ♀	[7]

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Table A.1 (*Continued*)

Product (date)	Trial features	Trial outcomes	Adherence outcomes	Refs.
	description): 273 FSW, 18 y+, recruited from bars. **Sites:** 1 (Yaounde, Cameroon). **Baseline characteristics:** A: 73% ≤29 y; M: >90% single; E: 49% primary, 93% could read; B: 84% ≥1; NP: 64% ≥ 4–7 PPW; C: 58% never use; FP: none >15%		reported N-9 + condom >75% acts	
N-9 film (1995–1996)	**Design and regimen:** Phase 3, RCT: N-9 film vs. PL, pa. **Intended outcome:** 88 endpoints → 50% HIV risk reduction. **Follow-up (retention rate):** μ 14 m FU; 73% ≥1 y (82% RET). **Cohort (number, description):** 1292 FSW, 18–45 y, μ ≥4 PPM. **Sites:** 2 (Yaoundé and Douala, Cameroon); estimated HIV incidence was 10%/y. **Baseline characteristics:** A: μ 26 y; M: 95–97% unmarried; E: 99% able to read; B: μ 1.4 living children; AI: 16–17% (ever); C: 48–49% with last client; FP: 86–87% none	N-9 not effective for prevention of NG, CT, HIV	Film + condom: 83–86% AWC, 63–69% AWP; film: 3–4% AWC, 15–18% AWP; condom only: 10–13% acts, AWP	[8]
N-9 gel [Advantage 24®] (1996–1998)	**Design and regimen:** Phase 3, RCT: N9 vs. PL (polycarbophil and carbomer base for N-9), 1 qd; re-apply within 24 h if douched/ cleaned the vagina. **Intended outcome:** NG/CT prevention [no info on SS calculation]. **Follow-up (retention rate):** median 50 w FU; (at 12 m: 61% [PL] and 69% [N9] RET). **Cohort (number, description):** 278 FSW, 18 y+, enrolled through	Significantly higher incidence of NG in N-9 group; no differences for other STDs (not powered for determining effect for syphilis or HIV)	Median compliance: 78% [0–100%]; 100% compliant: 34%; <25% compliant: 13%	[9]

	STD clinic attendance. **Sites:** 1 (Mombasa, Kenya); no information on incidence. **Baseline characteristics:** A: μ 28 y; M: 52% ever married; E: μ 7 y [0–15]; B: μ 1 live birth [0–8]; NP: μ 1 PPW [1–5]; CF: μ 2 APW [0–7]; C: 68–71% consistent (ND); FP: 44–55% none			
N-9 gel [Conceptrol®] (1998–2000)	**Design and regimen:** Phase 3, RCT, OL: N9 + condom vs. condom only; pa (≤1 h). **Intended outcome:** 90 endpoints → 90% STD (GC/CT) risk reduction. **Follow-up (retention rate):** 6 m FU (93% RET). **Cohort (number, description):** 1251 ♀; 18 y+, being treated for/with STD symptoms (excluding FSW). **Sites:** 20 (10 community clinics and 10 pharmacies in Younde, Cameroon). **Baseline characteristics:** A: μ 25 y; M: 65% unmarried/NLT; E: high education attainment (ND); B: 53–54% none; NP: μ 1 (last 30 d); CF: μ 3 (last 7 d); CLS: 63–65% did not use; FP: <5%	N-9 safe but not effective; lost to FU not differential by group; more acts with no protection in gel + condom group vs. condom only group	Gel: 76% of acts (63% with gel plus condom); condoms: 81%	[10]
N-9 vaginal gel (1996–2000)	**Design and regimen:** Phase 3 [design was Phase 2 B/3 but only Phase 3 data are included], RCT: N9 vs. PL (Replens® lubricant gel), pa (≤1 h). **Intended outcome:** 100 endpoints → 50% HIV risk reduction. **Follow-up (retention rate):** 48 w FU (71% RET at 24 w, 68% RET at 48 w). **Cohort (number, description):** 892 FSW, 18 y+ (16 y+ in South Africa), enrolled in STD clinics,	Did not show protective effect of N-9. Possible increased risk of HIV (stop further studies of N-9 as microbicide)	52–53 % ♀ reported gel ≥95% AWC; 31–34% reported gel = 100% AWC. Overall—79–81% AWC, 68–72% AWP; Cotonou, Benin—86–88% AWC, 57–65% AWP; Abidjan, Côte d'Ivoire—76–79% AWC, 29–36% AWP;	[11]

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Table A.1 (*Continued*)

Product (date)	Trial features	Trial outcomes	Adherence outcomes	Refs.
	sex-worker clinics, or truck stops (Durban). **Sites:** 4 (Cotonou, Benin [*n* = 259], Abidjan, Côte d'Ivoire [*n* = 188], Durban, South Africa [192], Hat Yai, Thailand [194]); estimated HIV incidence was 5%/y. **Baseline characteristics:** [Total] A: median 26 y; E: median 6 y; NP: median 3 clients/d; AI: 14% ever, mean 2 APW; C: ≈66% >50% clients, less than 15% >50% partners; FP: 17% OC, 14% injectable HC, 4% TL, 22% other. [Cotonou, Benin] A: 28 y; E: 7 y; NP: 3 clients/d; AI: 8% ever; C: 54% clients, 5% partners; FP: 10.5% hormonal, 50% other; [Abidjan, Côte d'Ivoire] A: 25 y; E: 9 y; NP: 4 clients/d; AI: 5% ever; C: 98% clients, 11% partners; FP: 7% OC, 32% other; [Durban, South Africa] A: 24 y; E: 6 y; NP: 4 clients/d; AI: 41%, 3×/w; C: 17% clients, 7% partners; FP:14% OC, 44% injectable HC, 7% other; [Hat Yai, Thailand] A: 26 y; E: 6 y; NP: 2 clients/d; AI: 4.4%, 1×/w; C: 100% clients, 14% partners; FP: 28% OC, 15% TL, 12% injectable HC		Durban, South Africa—76–84% AWC, 80–85% AWP; Hat Yai, Thailand—60–66% AWC; 29–36% AWP	
Carraguard vaginal gel (1999–2000)	**Design and regimen:** Phase 2, RCT: Carraguard vs. PL (methylcellulose), qod plus pa (≤1 h). **Intended outcome:** Detect 1.6× increase in genital findings with epithelial	Carraguard found safe and acceptable for use 3×/w for up to 1 y	87–96% ♀ returned at least 3 applicators/w (minimum adherence); μ 4 applicators/w	[12]

	disruption. **Follow-up (retention rate):** 1 y FU (90% RET). **Cohort (number, description):** 165 ♀, 18 y+, recruited from FP and general health clinics. **Sites:** 1 (Chiang Rai, Thailand). **Baseline characteristics:** A: μ 31–32 y; M: >95%; E: μ 6.4–7.2 y; B: 95% ≥1 live birth; NP: 2.4% >1; CF: μ 2.4–2.1 APW; AI: 0 (year before screening); C: 1–5% consistent (ND), 29–39% inconsistent (ND); FP: 92% using, 2/3 HC		(counting/ weighing used applicators). 84–91% sex acts with gel (SELF)	
Dextrin sulfate (DS) vaginal gel (2001)	**Design and regimen:** Expanded safety, 4-arm RCT: DS bid, PL (lactic acid, carbopol, sodium hydroxide, and purified water—base for DS gel) bid, DS pa, and observation only. Participants had to fill applicators prior to each application. **Intended outcome:** Safety. **Follow-up (retention rate):** 4 w FU (96% RET). **Cohort (number, description):** 109 ♀, 18–45 y (sex ≥2×/w), recruited from post-natal clinics near Nsambya Hospital. **Sites:** 1 (Kampala, Uganda). **Baseline characteristics:** A: μ 28 y; E: 55% completed primary; CF: 95% reported 2–3 APW	Results show satisfactory safety and acceptability profile of DS gel	89% of participants reported twice daily use during 28 d FU	[13]
Carraguard vaginal gel (1999–2002)	**Design and regimen:** Phase 2, RCT: Carraguard vs. PL, qod, plus pa (≤1 h). **Intended outcome:** Safety (powered to detect difference in rates of genital findings). **Follow-up (retention rate):** 6–12 m FU (77% RET). **Cohort (number, description):** 400 healthy, HIV negative ♀, 18 y+,	Safe, acceptable	Minimum adherence (≥9 applications/ m) = 85–97%. Gel use >80% sex acts (SELF)	[14]

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Table A.1 (*Continued*)

Product (date)	Trial features	Trial outcomes	Adherence outcomes	Refs.
	recruited from FP and general health clinics. **Sites:** 2 (Ga-Rankuwa, Gauteng and Gugulethu, Western Cape, South Africa). **Baseline characteristics:** A: μ 28 y [18–55]; M: 59% steady partner (NLT), 13–14% no steady partner; E: 89% ≥ secondary; B: 31% = 0, 34% = 1; NP: 7.5% had other partners; CF: not asked; FP: 54% injectable HC, 15–16% OC; 18–19% none			
Carraguard vaginal gel (2001–2002)	**Design and regimen:** Phase 1/2, RCT: Carraguard vs. PL (methylcellulose), pa (≤1 h); condom if perceived risk of STD/HIV. **Intended outcome:** Safety (powered to detect difference in genital findings). **Follow-up (retention rate):** 6 m FU (95% RET). **Cohort (number, description):** 55 low risk, monogamous couples, 18 y+. **Sites:** 1 (Chiang Rai, Thailand). **Baseline characteristics:** A: μ ♀ 31–34 y, μ ♂ 35–36 y; M: 100%; E: μ♀ 5–7 y [0–16], ♂ 6–7 y [0–14], B: μ 1.5–1.8 live births; NP: 1 (eligibility criteria); CF: 1.8–2 APW; C: 79–93% never, 7–21% inconsistent (ND); FP: 32–48% OC, 26–39% TL, 4–11% none	Safe for ♀ and ♂; acceptable	μ 91% adherence (sex acts with gel only, no condom) based on count/ weighing used applicators and ♀ SELF	[15]
Ortho® All-Flex® Arcing Spring Diaphragm (2003–2006)	**Design and regimen:** Phase 3, RCT: diaphragm + Replens® lubricant gel + condoms vs. condoms only; insert diaphragm any time before	Diaphragm had no protective benefit against HIV in addition to condoms and	Diaphragm ALS: 73% of the time (SELF)	[16]

	coitus and leave in place for 6 h after sex; condom pa; insert additional lubricant pa. **Intended outcome:** 5000 ♀ = 90% power → 33% HIV reduced risk. **Follow-up (retention rate):** μ 21 m [12–24] FU (93% RET). **Cohort (number, description):** 4948 ♀, 18–49 y, sex μ 4/m, recruited from community-based organizations, FP, well-baby and general health clinics; print ads, radio. **Sites:** 3 (Durban and Johannesburg, South Africa and Harare, Zimbabwe); estimated HIV incidence was 3.5–5%/y. **Baseline characteristics:** A: 38% ≤24 y, 39% 25–34 y; M: 59%; E: 43% ≥high school; NP: μ 2 [1–30] lifetime; CF: 35% >3×/w; C: 68% last sex act; FP: 25% injectable HC, 36% OC, 20% barrier method, 13% none	comprehensive HIV prevention program		
SAVVY® (C31 G) vaginal gel (2004–2006)	**Design and regimen:** Phase 3, RCT: SAVVY® vs. PL (HEC), pa (≤1 h). **Intended outcome:** 66 endpoints → 50% HIV risk reduction. **Follow-up (retention rate):** 12 m FU (85% RET); trial stopped early. **Cohort (number, description):** 2142 ♀ (≥3 APW, ≥2 PPM last 3 m), 18–35 y, not FSW per se (most exchanged sex for cash),recruited from markets, bars, hotels. **Sites:** 2 (Accra and Kumasi, Ghana); estimated HIV incidence was 5%/y. **Baseline characteristics:** A: μ 23 y (SD 3.6); M: 88% unmarried/NLT;	Stopped early due to lower than anticipated HIV incidence	Percentage usage in all sex acts in 7 d prior to visits (SELF): gel 75–77%, gel + condoms 70–72%, gel only 5%. Percentage usage of gel in all sex acts without condom was 43–47% (SELF)	[17]

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Table A.1 (*Continued*)

Product (date)	Trial features	Trial outcomes	Adherence outcomes	Refs.
	E: 76–77% ≤9 y; B: 73% ever pregnant, μ 2.1; NP: μ 6 PPM (last 30 days); CF: μ 9–10 APW; C: 40% CLS; FP: 46–48% condom, 37–40% none			
SAVVY® (C31 G) vaginal gel (2004–2006)	**Design and regimen:** Phase 3, RCT: SAVVY vs. PL (HEC gel), pa (≤1 h). **Intended outcome:** 66 endpoints → 50% HIV risk reduction. **Follow-up (retention rate):** 12 m FU (77% RET); trial stopped early. **Cohort (number, description):** 2153 ♀ (≥ 2 APW, ≥1 partner last 3 m) 18–35 y; from markets, bars, hostels, military barracks, colleges. **Sites:** 2 (Lagos and Ibadan, Nigeria); estimated HIV incidence was 5%/y. **Baseline characteristics:** A: μ 24 y (SD 3.7–3.8); M: 86% not married/NLT; E: 70–72% ≥9 y; B: 75% ever pregnant, μ 1.4; NP: μ 13 PPM, last month; CF: μ 9.5–9.6 APW; FP: 69–72% condom, <10% none	Stopped early due to lower than anticipated HIV incidence	Percentage usage in all sex acts in 7 d prior to visits (SELF): gel μ 78–79%, condom μ 87%, gel + condom 69–70%, gel only 4–5%. Gel used 62% of all sex acts (SELF)	[18]
Cellulose sulfate gel plus diaphragm (2004–2005)	**Design and regimen:** Phase 2, RCT (3-arm, partially blinded): diaphragm + CS gel vs. diaphragm + PL (K-Y® jelly) vs. CS gel alone, pa; apply gel in dome of diaphragm prior insertion, plus gel within 1 h BS (keep diaphragm 6–24 h); gel only: insert ≤1 h BS. **Intended outcome:** Safety and adherence. **Follow-up (retention rate):** 6 m FU (89% RET). **Cohort (number,**	High acceptability but only moderate adherence reported; consistent condom use and consistent product use were highly correlated	87% ♀ ever used diaphragm and 96% ever used gel; 71% ♀reported product LS: 66% diaphragm + gel and 80% gel only; 59% ♀ reported using product every act	[19]

	description): 119 ♀, 18–49 y, recruited from reproductive health/FP clinics. **Sites:** 1 (Harare, Zimbabwe). **Baseline characteristics:** A: μ 29 y; M: 97%; E: μ 10.3 y; C: 85% ever used, 38% LS; CF: median 5 APW [2–11]; FP: 72% OC, 26% injectable HC			
ACIDFORM vaginal gel plus diaphragm (2004–2005)	**Design and regimen:** Phase 2, RCT: ACIDFORM gel + diaphragm vs. PL (K-Y® jelly) + diaphragm, insert 1 dose gel after placement of diaphragm, new dose with each sex act, keep diaphragm in 6–24 h. **Intended outcome:** Safety and feasibility. **Follow-up (retention rate):** 6 m FU (82% RET). **Cohort (number, description):** 120 HIV-sexually-active ♀, 18–48 y, recruited from FP/community clinics and others. **Sites:** 1 (Yeoville, Johannesburg, South Africa). **Baseline characteristics:** A: μ 29.4 y; M:59% living with partner; E: μ 11 y; B: 86% ever pregnant; FP: 50% OC, 44% injectable HC	Trend toward more safety events in ACIDFORM gel group	Proper use reported for 94–98% of sex acts; 26 ♀ reported incorrect/ inconsistent use at some point during study	[20]
Praneem polyherbal vaginal tablet (2004–2006)	**Design and regimen:** Phase 2, RCT: Praneem gel vs. PL, pa (≤1/2 h). **Intended outcome:** Safety and acceptability. **Follow-up (retention rate):** 6 m FU (95% RET). **Cohort (number, description):** 100 sexually-active monogamous ♀, 18–45 y. **Sites:** 1 (Pune, India). **Baseline characteristics:** A: μ 30–31 y; M: 98–100%; E: 74–78% >4th grade; C: 92–96% inconsistent (ND)/never	Praneem found safe for coital use up to 6 m among low-risk ♀; ♀ reporting that gel interrupted sex were less likely to be adherent.	70.5% reported 100% adherence; 29.5% reported <100% adherence	[21] (see also [22])

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Table A.1 (*Continued*)

Product (date)	Trial features	Trial outcomes	Adherence outcomes	Refs.
Invisible Condom® vaginal gel (not published)	**Design and regimen:** Phase 2, RCT: PL (HEC gel) vs. polymer alone vs. polymer plus SLS (sodium lauryl sulfate), bid, ≤4 sex acts per each 14 days gel application, apply gel ≤1 h of planned sexual intercourse. **Intended outcome:** powered to detect AE rates >13%. **Follow-up (retention rate):** 8 w FU (77% RET). **Cohort (number, description):** 194 ♀, 18–49 y. **Sites:** 1 (Yaounde, Cameroon). **Baseline characteristics:** A: μ 30 y	Invisible Condom® formulations and applicator were well-tolerated when applied intravaginally bid for 2 w	70–86% compliance; however, only 20% of gel applications coincided with sex	[23]
Cellulose sulfate vaginal gel (2005–2007)	**Design and regimen:** Phase 3, RCT: CS gel vs. PL (HEC gel), pa (≤1 h). **Intended outcome:** 66 endpoints → 50% risk reduction [no info on SS calculation]. **Follow-up (retention rate):** 12 m FU (88% RET). **Cohort (number, description):** 1393 ♀, 18 y+, FSW at some sites (≥3 PPM, ≥3 APW), recruited via FSW peer education net-works, clinics. **Sites:** 5 (Cotonou, Benin [*n* = 227], Kampala, Uganda [*n* = 303], Durban, South Africa [*n* = 592], Chennai, India [*n* = 253], Bagalkot, India [*n* = 23]); estimated HIV incidence was 4%/y. **Baseline characteristics:** A: median 29 y; M: 22.9%; E: median 8 y; NP: median 10 CPM (last 3 m); CF: median 4 APW (last 7 d); AI: 3.7%	No protective effect shown. Interim results suggested possible increase in HIV risk (study stopped early)	Gel used in 87% of all sex acts of previous 7 d (SELF); condoms used in ≈95% of sex all acts; gel used in 45% of sex acts without condom. [Cotonou, Benin] gel use: 63% AWMP, 94% AWOP (last 7 d); [Kampala, Uganda] gel use: 60% AWMP, 85% AWOP (last 7 d); [Durban, South Africa] gel use: 91% AWMP, 95% AWOP (last 7 d); [Chennai, India] gel use: 38% AWMP, 91% AWOP (last 7 d);	[24]

	(last 1 m before screening); CLS: 61%; FP: 44.4% (HC, IUD, TL). [Cotonou, Benin] A: median 28 y; M: 0%; E: median 6 y; NP: median 125 CPM (3–840); CF: median 14 APW last 7 d; CLS: 72%; FP: 8 %; [Kampala, Uganda] A: median 25 y (18–48); M: 5%; E: median 7 y; NP: 180 CPM (3–1580); CF: median 21 (3–210); CLS: 87%; FP: 37%; [Durban, South Africa] A: median 31 y; M: 10%; E: median 10 y; NP: median 3 CPM (3–12); CF: median 4 (3–70); CLS: 38%; FP: 46%; [Chennai, India] A: median 35 y; M: 88% (41% NLT); E: median 7 y; NP: median 30 CPM (3–720); CF: median 5 (3–60); CLS: 75%; FP: 81%; [Bagalkot, India] A: median 28 y; M: 22% (all NLT); E: median 0 (0–10); NP: median 9 CPM (3–54); CF: median 3 (3–10); CLS: 78%; FP: 57%		[Bagalkot, India] gel use: 95% AWMP, 97% AWOP (last 7 d)	
Cellulose sulfate vaginal gel (2004–2007)	**Design and regimen:** Phase 3, RCT: CS gel vs. PL (HEC gel), pa (immediately before), re-apply if no sex within 1 h. **Intended outcome:** 66 events → 50% HIV reduction. **Follow-up (retention rate):** 1 y FU (70% RET). **Cohort (number, description):** 1644 ♀, 18–35 y, (≥3 APW; ≥1 partner within last 3 m). **Sites:** 2 (Lagos and Port Harcourt, Nigeria); estimated HIV incidence was 5%/y. **Baseline characteristics:** A: μ 23 y; M: 95% not married; E: μ 10 y; NP: 18–21 last 3 m (15–17 new); CF: 5–6 APW	Stopped early when other CS trial [24] stopped	Gel: 81% of all acts 7 d before monthly visit (50% of acts without condom) (SELF)	[25]

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Table A.1 (*Continued*)

Product (date)	Trial features	Trial outcomes	Adherence outcomes	Refs.
	(at 7 d before screening); CLS: 60–61% (past 7 d); FP: 55–57% condoms; 20–21% none			
Carraguard vaginal gel (2004–2007)	**Design and regimen:** Phase 3, RCT: Carraguard vs. PL (methylcellulose gel), pa (≤1 h sex). **Intended outcome:** 194 endpoints → 33% HIV reduction. **Follow-up (retention rate):** 9–24 m FU (68% RET). **Cohort (number, description):** 6202 ♀, 16 y+, recruited from general population. **Sites:** 3 (Gugulethu, Western Cape [*n* = 2315], Soshanguve, Gauteng [*n* = 2402], Isipingo, Durban, KwaZulu-Natal [*n* = 1485], South Africa); estimated HIV incidence was 3.5%/y. **Baseline characteristics:** A: *μ* 31 y; M: 63% SNM, >98% had steady partner; E: *μ* 11 y (0–15); B: 80–82% ever gave birth; NP: 9% had other partners; CF: *μ* 2 APW (2 w before screening); AI: 2% (last 3 m); CLS: 34% AWMP, 62% AWOP; FP: >50% injectable HC. [Gugulethu, Western Cape] A: *μ* 33 y; M: 54% SNM; E: *μ* 10.5 y; NP: 3% other partners; CF: 2.2 APW; AI: <1% (ever); CLS: 37% AWMP, 52% AWOP; FP: 60% HC; [Soshanguve, Gauteng] A: *μ* 29 y; M: 66% SNM; E: *μ* 11.5 y; NP: 16% other partners; CF: 2.2 APW; AI: 1% (ever); CLS: 34% AWMP, 67% AWOP; FP: 47% HC; [Isipingo, Durban, KwaZulu-Natal] A: *μ*	Carraguard gel safe, not effective for HIV prevention	Gel: *μ* 96% at LS (SELF); CLS: *μ* 64% (SELF); Primary adherence measure: *μ* 42% "covered" sex acts (*μ* weekly insertions, per dye stain assay/*μ* weekly sex acts (SELF). [Gugulethu, Western Cape] Gel: *μ* 95% at LS (SELF); CLS: *μ* 68% (SELF); *μ* 27% covered acts; [Soshanguve, Gauteng] Gel: *μ* 98% at LS (SELF); CLS: *μ* 59% (SELF); *μ* 48% covered acts; [Isipingo, Durban, KwaZulu-Natal] Gel: *μ* 92% at LS (SELF); CLS: *μ* 58% (SELF); *μ* 55% covered acts	[26]

	30 y; M: 74% SNM; E: μ 10.8 y; NP: 8% other partners; CF: 1.3 AW; AI: 6% (ever); CLS: 30% AWMP, 50% AWOP; FP: 44% HC			
PRO-2000 vaginal gel (2003–2004)	**Design and regimen:** Phase 2, RCT (4-arms): 0.5% PRO-2000 gel vs. 2% PRO-2000 gel vs. PL (HEC gel) vs. control (no gel), bid/28 d, women instructed to wash vagina with water before inserting gel as per normal hygiene practice. **Intended outcome:** Safety and acceptability. **Follow-up (retention rate):** 28 d FU (69% RET). **Cohort (number, description):** 180 healthy and symptomatic ♀, 18–45 y. **Sites:** 1 (Kampala, Uganda). **Baseline characteristics:** A: μ 29 y; M: no information; E: 56% primary, 38% secondary; CF: 86% 2–3 APW, 14% ≥4 APW	Gel was safe and well-tolerated for bid use/4 w (move to Phase 3 recommended)	Overall adherence: 69%	[27]
PRO-2000 vaginal gel (2005–2009)	**Design and regimen:** Phase 3, RCT: 0.5% PRO 2000/5 gel vs. 2% PRO 2000/5 gel vs. PL (HEC gel); pa (≤1 h sex). **Intended outcome:** 90% power → 40% reduction HIV incidence. **Follow-up (retention rate):** 52 w overall FU, 104 w FU in Uganda (81% RET). **Cohort (number, description):** 9385 ♀, 16 y+. **Sites:** 6 (Durban, South Africa [2391 ♀, 18 y+, general population], Johannesburg, South Africa [n = 2499 ♀, 18 y+, recruited from general population], Masaka, Uganda [840 HIV-negative ♀ with HIV+ partner], Mwanza,	Did not show protective effect of 0.5% or 2% PRO 2000/5. HIV incidence at 52 w (+6) censored for pregnancy was 4.6 (4.2–5.1)	Gel used in μ 89% of LS; 58% ♀ classified as consistent gel users (defined as [1] gel LS ≥92% visits, [2] returned ≥1 used applicator when appropriate, and [3] attended ≥7/13 visits unless pregnant /HIV+). [Durban, South Africa] 89% gel use; 58% ♀ as consistent users; Johannesburg, South Africa] 85% gel use; 49%	[28]

(*Continued*)

Table A.1 (*Continued*)

Product (date)	Trial features	Trial outcomes	Adherence outcomes	Refs.
	Tanzania [1146♀, 16 y+, recruited from recreational facilities], Africa Centre, KwaZulu-Natal, South Africa [1177 ♀, 18 y+, recruited from general population], Mazabuka, Zambia [1332 ♀, 18 y+, recruited from general population]); estimated HIV incidence was 4.0%/y. **Baseline characteristics: A:** μ 30 y; M: varied by site (see ahead); E: 23% ≥ secondary; NP: 1% >1 partner (last 1 w); CF: median 2 APW; AI: 1% (last 4 w); CLS: 57% (excludes 2% PRO 2000/5 gel arm); FP: 56% (effective method). [Durban, South Africa] A: μ 29 y; E: 31% ≥ secondary; NP: <0.5% >1 partner (last 1 w); CF: 2 APW; AI: 2% (last 4 w); CLS: 77%; FP: 65%; [Johannesburg, South Africa] A: μ 27 y; E: 44% ≥ secondary; NP: <0.5% >1 partner (last 1 w); CF: median 3 APW; AI: 1% (last 4 w); CLS: 71%; FP: 60%; [Masaka, Uganda] A: μ 32 y; E: 2% ≥ secondary; NP: 0% >1 partner (last 1 w); CF: median 1 APW; AI: <0.5% (last 4 w); CLS: 70%; FP: 27%; [Mwanza, Tanzania] A: μ 30 y; E: 5% ≥ secondary; NP: 3% >1 partner (last 1 w); CF: median 1 APW; AI: <0.5% (last 4 w); CLS: 33%; FP: 50%; [Africa Centre, KwaZulu-Natal, South Africa] A: μ 35 y; E: 20% ≥ secondary; NP: <0.5% >1		♀ as [consistent users; [Masaka, Uganda] 89% gel use; 59% ♀ as consistent users; [Mwanza, Tanzania] 92% gel use; 57% ♀ as consistent users; [Africa Centre, KwaZulu-Natal, South Africa] 94% gel use; 71% ♀ as consistent users; [Mazabuka, Zambia] 93% gel use; 68% ♀ as consistent users	

	partner (last 1 w); CF: median 2 APW; AI: 1% (last 4 w); CLS: 42%; FP: 50%; [Mazabuka, Zambia] A: μ 29 y; E: 7% ≥ secondary; NP: <0.5 >1 partner (last 1 w); CF: median 2 APW; AI: 1% (last 4 w); CLS: 20%; FP: 61%			
BufferGel and PRO-2000 vaginal gels (2005–2009)	**Design and regimen:** Phase 2/2 b, RCT (4-arm): BufferGel vs. PRO-2000 vs. PL (HEC gel) vs. no gel; 1 applicator pa (≤1 h). **Intended outcome:** 192 endpoints → 15.3–33% HIV risk reduction (to warrant further study). **Follow-up (retention rate):** 12–30 m FU, μ FU 20.4 m (93.6% RET). **Cohort (number, description):** 3101 ♀, 18 y+, ≥ 1 sex act (past 3 m), ≤2 sex acts/d (past 2 w). **Sites:** 8 (Blantyre, Malawi [*n* = 441], Lilongwe, Malawi [*n* = 596], Durban, South Africa [*n* = 702], Hlabisa, South Africa [*n* = 346], Philadelphia, PA, USA [*n* = 200], Kamwala, Zambia [*n* = 319], Chitungwiza, Zimbabwe [*n* = 260], Harare, Zimbabwe [*n* = 223]). **Baseline characteristics:** A: μ 26–27 y; M: 62–63%; E: 62–64% ≥ some secondary; CF: μ 2.8–3 acts (last 7 d); AI: 4–5% (ever), 1% (last 7 d); CLS: 67–69%; FP: 19–20% OC, 46–49% injectable HC. [Blantyre, Malawi] A: μ 26 y; E: 6% ≥ secondary; NP: 0% >1; CF: median 3 APW; AI : 1% (ever); CLS: 52%; FP : 87%; [Lilongwe, Malawi] A: μ 27 y; E: 3% ≥ secondary; NP: 0% >1; CF: median 2 APW;	Safe but not effective	81.1% at LS, 69.1% in sex acts without condom (SELF); Condom use similar in gel arms (72%) but higher in no gel arm (81%) (SELF). [Blantyre, Malawi] 82.6% gel at LS; 64.7% without condom; [Lilongwe, Malawi] 75.4% gel at LS; 68.7% without condom; [Durban, South Africa] 79% gel at LS; 63.5% without condom; [Hlabisa, South Africa] 79.2% gel at LS; 61.7% without condom; [Philadelphia, PA, USA] 76.7% gel at LS; 56% without condom; [Kamwala, Zambia] 82.5% gel at LS; 81.6% without condom; [Chitungwiza, Zimbabwe] 93.5% gel at LS; 89.9% without condom; [Harare,	[29]

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Table A.1 (*Continued*)

Product (date)	Trial features	Trial outcomes	Adherence outcomes	Refs.
	AI: 1% (ever); CLS: 55%; FP: 91%; [Durban, South Africa] A: μ 25 y; E: 39% ≥ secondary; NP: 4% >1; CF: median 2 APW; AI: 4% (ever); CLS: 77%; FP: 92%; [Hlabisa, South Africa] A: μ 25 y; E: 30% ≥ secondary; NP: 1% >1; CF: median 1 APW; AI: <1% (ever); CLS: 62%; FP: 75%; [Philadelphia, PA, USA] A: μ 35–36 y; E: 80% ≥ secondary; NP: 27% >1; CF: median 2 APW; AI: 46% (ever); CLS: 61%; FP: 89%; [Kamwala, Zambia] A: μ 23 y; E: 9% ≥ secondary; NP: 3% >1; CF: median 3 APW; AI: 3% (ever); CLS: 77%; FP: 98%; [Chitungwiza, Zimbabwe] A: μ 26 y; E: 29% ≥ secondary; NP: 3% >1; CF: median 5 APW; AI: 1% (ever); CLS: 87%; F: 99% [Harare, Zimbabwe] A: μ 27 y; E: 39% ≥ secondary; NP: 0% >1; CF: median 4 APW; AI: <1% (ever); CLS: 85%; FP: 99%		Zimbabwe] 91.0% gel at LS; 78.1% without condom	
1% tenofovir vaginal gel (2007–2010)	**Design and regimen:** Phase 2 b, RCT: 1% tenofovir gel vs. PL (HEC gel), 1 dose before sex (up to 12 h) plus 1 dose after sex (up to 12 h) and no more than 2 doses in 24 h (BAT24 regimen). **Intended outcome:** 92 endpoints → 90% power to detect 50% effect on HIV. **Follow-up (retention rate):** 30 m FU, monthly visits, μ 18 m FU per participant (95% RET). **Cohort (number,**	1% tenofovir gel reduced HIV risk by 39%; 54% in highly adherent women (defined as using gel in >80% sex acts)	Primary adherence measure: the proportion of sex acts covered by two doses of gel determined by monthly applicator count and SELF coital frequency. [eThekwini, KwaZulu-Natal, South Africa]	[30]

	description): 1085 ♀ enrolled and randomized, 18–40 y, sexually active (≥2 sex acts in last 30 d), HIV-uninfected; 889 ♀ analyzed. **Sites:** 2 (urban site: eThekwini, KwaZulu-Natal, South Africa [*n* = 278]; rural site: Vulindlela, KwaZulu-Natal, South Africa [*n* = 611]); estimated HIV incidence was 11.2%/y. **Baseline characteristics:** A: μ 24 y; M: 6% (88% stable partner); NP: μ 3–4 (lifetime); CF: 62% (last 7 d); AI: <0.5% (last 30 d); C: 29% always used; FP: 15% OC, 82% injectable HC. [eThekwini, KwaZulu-Natal, South Africa] A: μ 25; M: 4% (93% stable partner); NP: μ 6 (lifetime), 2.5% new partner (last 7 d); CF: 68.3% (last 7 d); AI: 0.4% (last 30 d); CLS: 42.8% always; FP: 79.9% injectable HC; [Vulindlela, KwaZulu-Natal, South Africa] A: μ 23; M: 6.5% (77% stable partner); NP: μ 2.1 (lifetime), 0.5% new partner (last 7 d); CF: 58.9% (last 7 d); AI: 0.5% (last 30 d); CLS: 22.9% always; FP: 83.1% injectable HC		median primary adherence: 50.0%; median SELF adherence: 84.0%; [Vulindlela, KwaZulu-Natal, South Africa] median primary adherence: 68.7%; median SELF adherence: 92.9%	
1% tenofovir vaginal gel (2006–2007)	**Design and regimen:** Phase 2, RCT (4-arms): tenofovir gel (qd) vs. PL (HEC gel, qd) vs. tenofovir gel (pa) vs. PL (pa). **Intended outcome:** Safety and acceptability. **Follow-up (retention rate):** 6 m FU (96% RET). **Cohort (number, description):** 200 sexually-active ♀. **Sites:** 3 (India [*n* = 100], Birmingham,	1% tenofovir gel was safe and acceptable for qd use by HIV-negative ♀ over extended periods of time	80% adherence for coitally dependent use within 2 h of sex; 83% adherence of qd doses used. [India] 93% sex acts with gel use last 1 m (pa regimen); 72% gel used/d (qd regimen);	[31]

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Table A.1 (*Continued*)

Product (date)	Trial features	Trial outcomes	Adherence outcomes	Refs.
	NY, USA [2 sites; *n* = 100]. **Baseline characteristics: A:** μ 32 y; M: 64%. [India] A: μ 33 y; M: 99%; E: 21% > 10 y; [Birmingham, NY, USA] A: μ 31; M: 28%; E: 63% > 12 y		[Birmingham, NY, USA] 80% sex acts with gel use in last 1 m (pa regimen); 75.5% gel used/day (qd regimen)	
Oral and topical tenofovir (2008–2010)	**Design and regimen:** Phase 2, OL (tenofovir tablet and gel), cross-over, 3 regimens: oral tablet qd × 3 w vs. vaginal gel qd × 3 w vs. both qd × 3 w, 1 w wash-out before cross-over, randomized to regimen order. **Intended outcome:** Adherence and acceptability. **Follow-up (retention rate):** 21 w FU (97–100% RET per visit). **Cohort (number, description):** 168 ♀, 18–45 y, sexually active (sex ≥4× during 1 m before screening). **Sites:** 7 (South Africa [*n* = 48], Uganda [*n* = 24], United States [*n* = 72]). **Baseline characteristics:** A: μ 30.8 y; M: 40%; E: >60% ≥ secondary; NP: μ 1.4 (last 3 m); CF: 33% ≥3 APW (last 3 w); AI: 27% (ever); CLS: 48%. [South Africa] A: μ 31; M: 40%; E: 58% ≤ primary; NP: μ 1 (last 3 m); CF: 33% ≥3 APW (last 3 w); AI: 2%; CLS: 62%; [Uganda] A: μ 30; M: 96%; E: 87% ≤ primary; NP: μ 2.6 (last 3 m); CF: 71% ≥3 APW (last 3 w); AI: 0% (ever); CLS: 21%; [United States] A: μ 31; M: 21%; E: 81% attended college; NP: μ 1.2 (last 3 m); CF: 21% ≥3 APW (last 3 w); AI: 53% (ever); CLS: 48%	SELF adherence was 94% vs. 62–64% per serum levels; US ♀ favored tablet (72%), African ♀ had mixed preference (42% gel, 40% tablet)	94% (SELF); only 64% of women had serum levels consistent with taking a daily tablet. [South Africa] 39–44% (drug level), 59–60% inconsistent with drug levels by SELF; [Uganda] 39–50% (drug level), 50–58% inconsistent with drug levels by SELF; [United States] 81–84% (drug level), 8–14% inconsistent with drug levels by SELF	[32]

Oral and topical tenofovir and oral Truvada®[a] (2009–2012)	**Design and regimen:** Phase 3, RCT, double-blind (5-arms): oral tenofovir vs. oral Truvada® vs. PL (tablet) vs. 1% tenofovir gel vs. PL (HEC gel), qd. **Intended outcome:** HIV prevention. **Follow-up (retention rate):** ND. **Cohort (number, description):** 5029 ♀, HIV negative, heterosexual. **Sites:** 5 (South Africa [3 sites; m = 4077], Uganda [*n* = 322], Zimbabwe [2 sites; *n* = 630]). **Baseline characteristics:** [South Africa] A: *μ* 25 y; M: 8%; E: 54% ≥ secondary; [Uganda] A: *μ* 28 y; M: 50%; E: 3% ≥ secondary; [Zimbabwe] A: *μ* 28 y; M: 94%; E: 60% ≥ secondary	No effectiveness found; adherence was very low (≈30% of ♀ never had any drug detected)	In a subsample of 773 participants, <1 out of 3 had drug detected in blood sample	[33]
Dapivirine vaginal ring (2010)	**Design and regimen:** Phase 2, RCT: dapivirine (25 mg) platinum catalyzed silicone vaginal ring vs. PL (non-medicated platinum catalyzed silicone vaginal ring), 1:1 randomization, wear ring for 3 consecutive 28-day periods, new ring each 28-day period, ring not to be removed between study visits. **Intended outcome:** Safety, acceptability, adherence and pharmacokinetics. **Follow-up (retention rate):** ND. **Cohort (number, description):** 280 ♀, HIV negative, healthy, sexually active. **Sites:** 10 (Kenya, Malawi, Tanzania, South Africa). **Baseline characteristics:** A: *μ* 26 y [18–40]; M: 22%; NP: 99% = 1 partner, 35% live with partner	Ring was safe and acceptable	SELF: 84% perfect adherence (ring never out); 92% with 100% daily adherence (ring never out ≥1 day); no clear relationship observed between plasma concentrations and residual amounts of dapivirine in used rings	[34–35]

Abbreviations: →, to measure; ♀, women; ♂, men; *μ*, mean/average; A, age; AE, adverse effects; AI, anal intercourse; ALP, after last partner; ALS, at last sex act;

APW, acts per week; AWC, acts with clients; AWMP, acts with main partner; AWOP, acts with other partners; AWP, acts with partners; B, parity; bid, twice per day; BS, before sex; C, condom; CF, coital frequency; CLS, condom at last sex; CPM, clients per month; CS, cellulose sulfate; CT, *Chlamydia trachomatis*; d, day; DS, dextrin sulfate; DSMC, Data and Safety Monitoring Committee; E, education; FP, contraception; FSW, female sex worker; FU, follow-up; h, hour; HC, hormonal contraception; HEC, hydroxyethylcellulose; LS, last sex; M, married/marital status; m, month; N-9, nonoxynol-9; ND, not defined; NG, *Neisseria gonorrhea*; NLT, not living together; NP, number of partners; OC, oral contraceptives; OL, open label; pa, per sex act; PL, placebo; PPM, partners per month; PPW, partners per week; qd, daily/once per day; qod, every other day; RCT, randomized controlled trial; RET, retention; SD, standard deviation; SELF, self-report; SNM, single/never married; SS, sample size; STD, sexually transmitted diseases; TL, tubal ligation; w, week; y, year.
[a]Truvada®—oral emtricitabine/tenofovir disoproxil fumarate combination tablet (Gilead Sciences, Foster City, CA, USA).

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