APPENDIX

Cost-effectiveness of long-acting injectable HIV pre-exposure prophylaxis in the United States

Neilan *et al.*

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Appendix Methods

HIV Prevention Trials Network (HPTN) 083 trial enrollment criteria

Inclusion criteria (1) included self-report of ≥1 of the following in the 6 months prior to enrollment:

1) any condomless receptive anal intercourse;
2) >5 sexual partners;
3) any stimulant drug use;
4) rectal or urethral gonorrhea or chlamydia or incident syphilis;
5) SexPro score of ≤16 (52)

Estimated population sizes

Estimated HIV prevalence is 15% (12) among 4.5 million (11) men who have sex with men (MSM) in the United States (US) (*i.e.,* 689,600 MSM with HIV and 3.8 million MSM without HIV, Appendix Table 1, below). Estimates for the size of the HIV pre-exposure prophylaxis (PrEP)-eligible population among MSM have increased over time (53–55). Based on National HIV Behavior Surveillance estimates of condomless anal sex among all MSM with a casual partner (46.7%) (56) and American Men's Internet Survey estimates of PrEP eligibility (51.4%) (55), we assumed that 50% of all MSM and transgender women (TGW) without HIV in the US are at high risk for HIV (HR) and are eligible for PrEP (*i.e.*, 1.9 million). While this estimate is larger than other estimates (53–55), we favored using a broad population for several reasons: to contrast with the smaller subset of the US HIV Prevention Trials Network (HPTN) 083 trial-based cohort; to account for a larger population that might include TGW (approximately 1 million) (57); given that we anticipate Food and Drug Administration (FDA) approval of CAB-LA for PrEP will not have strict eligibility criteria; and given the view of the HIV Medical Association that anyone who

68 considers themselves PrEP-eligible should be prescribed PrEP if medically eligible, regardless
69 of disclosed risk factors (58).
70
71 Based on National HIV Behavior Surveillance reported rates of any bacterial sexually
72 transmitted infection (17.6%) in the last 12 months, and condomless insertive and receptive anal
73 intercourse in the last 3 months (21.0%) (56), we assumed that 25% of the PrEP-eligible
74 MSM/TGW at HR are at very high risk for HIV (VHR). We assumed this subpopulation of
75 MSM/TGW was at higher risk for HIV compared to other PrEP-eligible MSM and were
76 representative of the US subset of HPTN 083 trial participants, who experienced a high off PrEP
77 trial incidence (estimated to be 5.32/100PY (1) vs. 0.51/100PY (12) among all MSM in the US).
78 Those willing to participate in a trial of injectable PrEP may also find oral PrEP burdensome and
79 have poorer adherence to PrEP.
80
81 **Assumptions related to transmissions**
82 Given that the proportion of the US population that would have enrolled in HPTN 083 is
83 uncertain, as well as the proportion of transmissions arising from this population, we varied
84 these parameters widely. We grounded the analysis in data from Singh *et al.*, which provides
85 both an estimate of absolute numbers of transmissions arising from MSM in 2015 (24,300 to
86 28,200, upper limit used in base case) as well as an incidence rate, 0.44 to 0.58/100PY (*i.e.*, a
87 denominator) (12). Based on the population estimates above and retaining the simplifying
88 assumptions that population size and transmissions remain constant over a 10-year horizon, we
89 calculated that 70% of new incident infections among all MSM are attributable to the all PrEP-
90 eligible HR population (19,700), and that 90% of those newly incident cases among the HR
91 population are attributable to the subset of the VHR population (17,800); thus, 63% of total
92 infections among MSM would be attributable to the VHR population.

Appendix Table 1. Derivation of modeled cohort population sizes

Parameter	Value	Source
US MSM (n)	4,503,100	(11)
HIV prevalence (%)	15.3	(12)
Estimated cohort size by characteristics, n		
MSM with HIV	689,600	Derived from (12), assumption
MSM without HIV	3,813,500	Derived from (11,12), assumption
MSM/TGW at HR, without HIV	1,906,800	Derived from (11,12), assumption
MSM/TGW at VHR, without HIV	476,700	Derived from (11,12), assumption

HR, high risk for HIV; MSM, men who have sex with men; TGW, transgender women; US, United States; VHR, very high risk for HIV.

Modeled population age

Using 100,000 simulations of a normal distribution with a mean of 30.1 years, range of 18-65 years, and standard deviation (SD) of 9.2 years, we fit these data to approximate the initial age model parameters. In the model, each simulated individual is then assigned an age at model start drawn from these estimated age parameters.

Baseline ART adherence, virologic suppression, and loss to HIV care

Details of the approach to specify the relationship between adherence level and the following treatment outcomes have been previously published: probability of HIV RNA suppression at 6 months after treatment initiation, monthly probability of subsequent viral rebound, and monthly probability of loss to follow-up (59-61). To model ART adherence, we used medication possession ratio (MPR) data from a database of private patients (47) and used the adherence

distributions: 3.8% of the cohort with ART adherence <70%, 6.1% with ART adherence between 70%-80%, 19.2% with ART adherence between 80-90%, and 70.8% of the cohort with ART adherence ≥90%. We fit these data to a logit-normal distribution using the procedure outlined in the supplement of Ross *et al., Clin Infect Dis* 2015 (60).

To model initial virologic suppression and late virologic failure, we used a trial evaluating the efficacy of dolutegravir which reported that, of 390 patients at 48 weeks, 361 remained suppressed and at 96 weeks, 339/371 remained suppressed, when censoring for patients who were considered to have virologic failure but may not have actually failed (*i.e.*, withdrawal, lost to care, *etc.*) (49). We then used the ratio of these two points (98.7%) to estimate the probability of late failure at 96 weeks to adjust for those withdrawn or lost to care. Applying the relationship between MPR, adherence level, and virologic suppression, derived above to this data source, these calculations resulted in those with adherence <5% having 100% monthly probability of late failure, those with moderate adherence (5-59%) having monthly late failure probability of 0.3-77% (annual probability of 3.6-99%), and those with the adherence ≥60% experiencing a monthly probability of late failure of 0.01% (annual probability of 0.12%).

To capture the loss to follow-up among patients, we assumed that those with the highest adherence (MPR >95%) had a monthly probability of loss to follow-up of 0.01% (annual probability of 0.12%), which would lead to approximately 4.5% of those with the highest adherence experiencing a loss to follow-up event in their lifetime. Then, we fit the distribution so that 74.03% of patients remained in care after 48 months, a value based on HIV Research Network data (50); those with the lowest adherence (MPR <5%) experience a monthly probability of loss to follow-up of 6.8% (annual probability of 57%). Those with moderate

adherence (MPR 5-94%) experience a monthly probability of loss to follow-up that is linearly interpolated between the maximum and minimum loss to follow-up estimates described above.

Generic oral emtricitabine/tenofovir disoproxil fumarate (F/TDF) adverse events

To capture the potential decreased quality-of-life from generic vs. branded tenofovir-based PrEP regimens, we modeled an extreme quality-of-life decrement to tip the scales in favor of branded emtricitabine/tenofovir alafenamide (F/TAF) based on prior work (8,60). A meta-analysis of more than 9,900 F/TDF PrEP recipients reported four grade 3-4 creatinine elevations (though these elevations were not statistically different from placebo controls) (8,60,61). To err on the side of overstating the adverse consequences of generic F/TDF, we assumed that 0.04% (4/9,900) (61) of the generic F/TDF population had immediate, irreversible end-stage renal disease, lasting all 10 years of the treatment period, with a persistent 47% reduction in quality-of-life (17). We also assumed 2% of the population experienced an osteoporosis-related fracture (15), leading to one year with a 30% decrement in quality-of-life (18). We assumed that all F/TDF-related fractures had the attributable cost of a hip fracture updated to 2020 USD ($76,400) (62). We also assumed that end-stage renal disease resulted in annual hemodialysis cost of $102,300 (reported value, updated to 2020 USD) (63). The costs of F/TDF-related fractures and end-stage renal disease were summed for all expected adverse event cases over the 10-year horizon. The annual cost increase, per individual affected by an adverse event related to generic F/TDF, was then calculated to be $4,100 (8).

Costs

PrEP program costs

PrEP program costs included: drug, clinic visit, administration for injections (CAB-LA only), and laboratory testing.

Drug

Generic F/TDF price was based on the wholesale acquisition cost from RedBook: $360/year (22). We used the lowest available published pricing of F/TDF based on Redbook (we assume that the pricing listed on the NAC FSS will continue to decrease). For branded F/TAF, we used the unit price for a 30-day supply from the National Acquisition Center Federal Supply Schedule (NAC FSS, $16,800/year) (23). Since CAB-LA + long-acting rilpivirine (CAB-LA/RPV-LA) combination injections prices recently became available (and CAB-LA pricing alone is not yet available), we used the reported wholesale acquisition cost (WAC) to inform our assumptions (24): We applied the price ratio of branded F/TAF from NAC FSS to the WAC branded F/TAF price to estimate the upper bound of an annual drug price for CAB-LA ($25,850/year) – 154% and 718% higher than branded and generic F/TDF, respectively (22–24).

Clinic costs

For clinic visits, defined by the Centers for Medicare and Medicaid Services (CMS) as “office or outpatients visits for established patients,” (26) we used the average non-facility price limiting charge for level 3 and level 4 physician visits (15 and 25 minutes, respectively) from 113 different US localities (Current Procedural Terminology (CPT) code 99203 or 99204 for an initial visit and 99213 or 99214 for subsequent visits) (25). For individuals prescribed oral PrEP, we assumed physician visits are recommended every 3 months ($420/year). We assumed CAB-LA would require physician visits every 2 months ($630/year) (1).

Laboratory and injection costs

For CAB-LA injection administration costs (6 times annually), we used the average price limiting charge from the same US localities in the CMS physician fee schedule (CPT 96372), yielding an

annual cost of $97 (25). For patients starting or already on generic F/TDF or branded F/TAF, we estimated biannual screening costs using serum creatinine (CPT code 82565), and urinalysis testing (CPT code 81005), yielding an annual cost of $15 (26). For patients starting or already on CAB-LA, we estimated biannual screening costs using serum creatinine (CPT code 82565), and liver function panel (CPT code 80076), yielding an annual cost of $27 (26).

Integrase inhibitor resistance

In scenario analyses, we examined the impact of integrase inhibitor resistance among all individuals with HIV who have taken CAB-LA for PrEP. All individuals acquiring HIV receive genotype testing. Individuals with HIV who have integrase inhibitor resistance are prescribed efavirenz-based or rilpivirine-based first-line ART regimens, which have lower probabilities of initial and sustained virologic suppression. To account for regional epidemiology of non-nucleoside reverse transcriptase inhibitor resistance, we also examined a scenario wherein all individuals who have acquired integrase inhibitor resistance while prescribed injectable PrEP receive a protease inhibitor-based drug as first-line ART.

Appendix Table 2. Additional input parameters for a cost-effectiveness analysis of CAB-LA vs. generic F/TDF and branded F/TAF for HIV PrEP among MSM/TGW in the US

Parameter	Value	**Range**	Source
Characteristics among those acquiring HIV			
Acute phase duration (months)	2		(64,65)
HIV RNA setpoint, distribution (% of cohort)			(66)
>100,000 copies/ml	25		
30,001-100,000	25		
10,001-30,000	25		
3,001-10,000	16		
≤3,000	9		
Upon incident HIV infection, baseline ART adherence and virologic suppression			
Adherence to ART (% of cohort)			(47)
≥90%	70.8	50-100	
80-89%	19.2		
70-79%	6.1		
<70%	3.7		
Integrase inhibitor-based ART efficacy (% achieving suppression)			(19,43)
≥90%	93	85.8-100	
80-89%	88		
70-79%	77		
<70%	59		

Appendix Table 2 continued. Additional input parameters for a cost-effectiveness analysis of CAB-LA vs. generic F/TDF and branded F/TAF for HIV PrEP among MSM/TGW in the US

Parameter	Value	**Range**	Source
Late virologic failure, annual probability ‡			(48,49)
≥60%	0.0012	0.0011-0.0013	
5-59%	0.036-1	0.032-1	
<5%	1		
Retention in HIV treatment			
Loss to HIV care, range by adherence level (annual probability) ‡			(50)
≥95%	0.0012	0.0006-0.0013	
5-94%	0.031-0.57	0.016-0.83	
<5%	0.57	0.34-0.83	
Opportunistic infections off ART, range by CD4 cell count (annual probability) ‡			(67)
Pneumocystis pneumonia	0.047-0.096	0.0024-0.18	
Mycobacterium avium complex	0.0012-0.055	0.0006-0.11	
Toxoplasmosis	0.0006-0.012	0.0003-0.06	
Cytomegalovirus	0.0012-0.094	0.0006-0.18	
Fungal infection	0.0012-0.038	0.0006-0.074	
Other opportunistic infection	0.0072-0.13	0.0036-0.24	

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Appendix Table 2 continued. Additional input parameters for a cost-effectiveness analysis of CAB-LA vs. generic F/TDF and branded F/TAF for HIV PrEP among MSM/TGW in the US

Parameter	Value	**Range**	Source
HIV-related mortality			
Chronic AIDS death by CD4 cell count, range by OI history (annual probability) ‡			(67)
>500 cells/μL	0.0030		
351–500	0.007		
201–350	0.011-0.28		
101–200	0.03-0.33		
50–100	0.040-0.33		
<50	0.16-0.58		
Non-AIDS death by age, in years (annual probability) ‡			(67)
18-19	0.00084		
20-24	0.0012		
25-29	0.0013		
30-39	0.0017-0.0023		
40-49	0.0031-0.0043		
50-59	0.007-0.0098		
60-69	0.016-0.024		
70-79	0.038-0.054		
80-99	0.077-0.15		

Appendix Table 2 continued. Additional input parameters for a cost-effectiveness analysis of CAB-LA vs. generic F/TDF and branded F/TAF for HIV PrEP among MSM/TGW in the US

Parameter	Value	Range	Source
HIV testing *			
Sensitivity, acute (%)	81.2		(68)
Sensitivity, chronic (%)	99.9		(69)
Specificity (%)	99.9		(70)
Frequency, Off PrEP (annual probability) † ‡	0.20		(1)
Costs (USD 2020)			
CD4 cell count test	62		(26)
HIV RNA test	112		(26)
Routine HIV care, annual, by CD4 count and ART status			(30,71,72)
>500 cells/μL	3,300 – 3,700		
351–500	4,500 – 6,500		
201–350	6,700 – 7,100		
101–200	7,700 – 13,500		
50–100	15,000 – 17,100		
<50	13,800 – 32,600		
Acute OI events	9,500 – 43,800		(26,30,71,72)
Death			(26,30,71,72)
OI-related	59,800		
HIV-related (excluding OI)	46,900		

AIDS, acquired immune deficiency syndrome; ART, antiretroviral therapy; CAB-LA, long-acting injectable cabotegravir HIV, human immunodeficiency virus; F/TAF, emtricitabine/tenofovir alafenamide fumarate; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HIV, human immunodeficiency virus; MSM, men who

have sex with men; OI, opportunistic infection; PY, person-year; PrEP, pre-exposure prophylaxis; RNA, ribonucleic acid; TGW, transgender women; USD, United States dollars.

* A fourth generation HIV antigen/antibody screen was modeled.

† Rates of HIV testing that occurred outside of the PrEP program were based on times to HIV detection from infection (41 months) reported by the United States Centers for Disease Control and Prevention (10), after using the model to account for detection upon presentation of opportunistic infection.

‡ Monthly probabilities were used in the model.

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Appendix Table 3. Scenario analysis: Integrase resistance for individuals in the CAB-LA strategy who acquire HIV and receive an efavirenz-based regimen as first-line ART

Strategy	Total Transmissions, n	Total QALY	Incremental QALY	Total cost, billion*	Incremental cost, billion*	ICER, $/QALY*
MSM at VHR (n = 476,700)						
Generic F/TDF	122,000	4,626,000	--	30.67	--	--
No PrEP	178,000	4,529,000	(97,000)	33.48	2.81	Excluded
Branded F/TAF	122,000	4,628,000	99,000	60.42	26.94	Excluded
CAB-LA	107,000	4,661,000	33,000	*72.89*	*12.47*	*1,188,000*
MSM at HR (n = 1,906,800)						
No PrEP	197,000	16,864,000	--	39.57	--	--
Generic F/TDF	135,000	16,982,000	118,000	44.72	5.15	44,000
Branded F/TAF	135,000	16,991,000	9,000	160.15	115.43	Excluded
CAB-LA	119,000	17,030,000	39,000	*222.68*	*62.53*	*3,726,000*

CAB-LA, long-acting injectable cabotegravir; F/TAF, tenofovir alafenamide fumarate-emtricitabine; F/TDF, tenofovir disoproxil fumarate-emtricitabine; HR, high risk for HIV; ICER, incremental cost-effectiveness ratio; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life-year; TGW, transgender women; 2020 USD, 2020 US dollars; VHR, very high risk for HIV.

* All economic outcomes are reported in 2020 US dollars. CAB-LA economic outcomes (in italics) were modeled using upper bound drug price of CAB-LA (price $25,850).

Strategies are listed in order of increasing cost per cost-effectiveness convention, and increments are expressed compared to the next less costly strategy; the order of strategies may differ throughout this analysis. Results are discounted at 3 percent per year and rounded to the nearest thousand. The ICER is the difference in cost divided by the difference in life expectancy for each strategy compared with the next less costly strategy. Strategies which are “Excluded” represent either a scenario where the strategy costs more and accrues fewer QALYs (as in No PrEP) or is a less efficient use of resources than the combination of two other strategies (as in branded F/TAF, also called extended dominance). The ICER for CAB-LA in italics represents the comparison to generic F/TDF.

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Appendix Table 4. Scenario analysis: Integrase resistance for individuals in the CAB-LA strategy who acquire HIV and receive a rilpivirine-based regimen as first-line ART

Strategy	Total Transmissions, n	Total QALY	Incremental QALY	Total cost, billion*	Incremental cost, billion*	ICER, $/QALY*
MSM at VHR (n = 476,700)						
Generic F/TDF	122,000	4,626,000	--	30.67	--	--
No PrEP	178,000	4,529,000	(97,000)	33.48	2.81	Excluded
Branded F/TAF	122,000	4,628,000	99,000	60.42	26.94	Excluded
CAB-LA	107,000	4,654,000	33,000	*72.77*	*12.36*	*1,585,000*
MSM at HR (n = 1,906,800)						
No PrEP	197,000	16,864,000	--	39.57	--	--
Generic F/TDF	135,000	16,982,000	118,000	44.72	5.15	44,000
Branded F/TAF	135,000	16,991,000	9,000	160.15	115.43	Excluded
CAB-LA	119,000	17,022,000	31,000	*222.57*	*62.42*	*4,447,000*

CAB-LA, long-acting injectable cabotegravir; F/TAF, tenofovir alafenamide fumarate-emtricitabine; F/TDF, tenofovir disoproxil fumarate-emtricitabine; HR, high risk for HIV; ICER, incremental cost-effectiveness ratio; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life-year; TGW, transgender women; 2020 USD, 2020 US dollars; VHR, very high risk for HIV.

* All economic outcomes are reported in 2020 US dollars. CAB-LA economic outcomes (in italics) were modeled using upper bound drug price of CAB-LA (price $25,850).

Strategies are listed in order of increasing cost per cost-effectiveness convention, and increments are expressed compared to the next less costly strategy; the order of strategies may differ throughout this analysis. Results are discounted at 3 percent per year and rounded to the nearest thousand. The ICER is the difference in cost divided by the difference in life expectancy for each strategy compared with the next less costly strategy. Strategies which are “Excluded” represent either a scenario where the strategy costs more and accrues fewer QALYs (as in No PrEP) or is a less efficient use of resources than the combination of two other strategies (as in branded F/TAF, also called extended dominance). The ICER for CAB-LA in italics represents the comparison to generic F/TDF.

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Appendix Table 5. Scenario analysis: Integrase resistance for individuals in the CAB-LA strategy who acquire HIV and receive a protease-inhibitor based regimen as first-line ART

Strategy	Total Transmissions, n	Total QALY	Incremental QALY	Total cost, billion*	Incremental cost, billion*	ICER, $/QALY*
MSM at VHR (n = 476,700)						
Generic F/TDF	122,000	4,626,000	--	30.67	--	--
No PrEP	178,000	4,529,000	(97,000)	33.48	2.81	Excluded
Branded F/TAF	122,000	4,628,000	99,000	60.42	26.94	Excluded
CAB-LA	107,000	4,661,000	33,000	*76.17*	*15.75*	*1,585,000*
MSM at HR (n = 1,906,800)						
No PrEP	197,000	16,864,000	--	39.57	--	--
Generic F/TDF	135,000	16,982,000	118,000	44.72	5.15	44,000
Branded F/TAF	135,000	16,991,000	9,000	160.15	117.85	Excluded
CAB-LA	119,000	17,022,000	31,000	*226.79*	*66.64*	*4,564,000*

CAB-LA, long-acting injectable cabotegravir; F/TAF, tenofovir alafenamide fumarate-emtricitabine; F/TDF, tenofovir disoproxil fumarate-emtricitabine; HR, high risk for HIV; ICER, incremental cost-effectiveness ratio; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life-year; TGW, transgender women; 2020 USD, 2020 US dollars; VHR, very high risk for HIV.

* All economic outcomes are reported in 2020 US dollars. CAB-LA economic outcomes (in italics) were modeled using upper bound drug price of CAB-LA (price $25,850).

Strategies are listed in order of increasing cost per cost-effectiveness convention, and increments are expressed compared to the next less costly strategy; the order of strategies may differ throughout the paper. Results are discounted at 3 percent per year and rounded to the nearest thousand. The ICER is the difference in cost divided by the difference in life expectancy for each strategy compared with the next less costly strategy. Strategies which are “Excluded” represent either a scenario where the strategy costs more and accrues fewer QALYs (as in No PrEP) or is a less efficient use of resources than the combination of two other strategies (as in branded F/TAF, also called extended dominance). The ICER for CAB-LA in italics represents the comparison to generic F/TDF.

Appendix Table 6. Model-projected 10-year clinical, cost and cost effectiveness outcomes of CAB-LA vs. generic F/TDF and branded F/TAF for HIV PrEP among MSM/TGW in the US (excluding the impact of renal disease and bone fracture adverse events)

Strategy	Total Transmissions, n	Total QALY	Incremental QALY	Total cost, billion*	Incremental cost, billion*	ICER, $/QALY*
MSM/TGW at VHR (n=476,700)						
Generic F/TDF	122,000	4,626,000	--	30.05	--	--
No PrEP	178,000	4,529,000	(97,000)	33.48	3.43	Excluded
Branded F/TAF	122,000	4,628,000	99,000	60.41	26.93	Excluded[†]
CAB-LA	107,000	4,654,000	26,000	*75.84*	*15.42*	*1,750,000*
MSM/TGW at HR (n=1,906,800)						
No PrEP	197,000	16,864,000	--	39.57	--	--
Generic F/TDF	135,000	16,982,000	118,000	42.24	2.67	21,000
Branded F/TAF	135,000	16,991,000	9,000	160.09	117.85	Excluded[‡]
CAB-LA	119,000	17,022,000	31,000	*226.32*	*66.24*	*5,936,000*

CAB-LA, long-acting injectable cabotegravir; F/TAF, tenofovir alafenamide fumarate-emtricitabine; F/TDF, tenofovir disoproxil fumarate-emtricitabine; HR, high risk for HIV; ICER, incremental cost-effectiveness ratio; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life-year; TGW, transgender women; 2020 USD, 2020 US dollars; VHR, very high risk for HIV.

* All economic outcomes are reported in 2020 US dollars. CAB-LA economic outcomes (in italics) were modeled using upper bound drug price of CAB-LA (price $25,850).

† Compared to branded F/TAF, CAB-LA has an incremental cost-effectiveness ratio of $589,000/QALY among MSM/TGW at VHR.

‡ Compared to branded F/TAF, CAB-LA has an incremental cost-effectiveness ratio of $2,136,000/QALY among MSM/TGW at HR.

Strategies are listed in order of increasing cost per cost-effectiveness convention, and increments are expressed compared to the next less costly strategy; the order of strategies may differ throughout this analysis. Results are discounted at 3 percent per year and rounded to the nearest thousand. The ICER is the difference in cost divided by the difference in life expectancy for each strategy compared with the next less costly strategy. Strategies which are “Excluded” represent either a scenario where the strategy costs more and accrues fewer QALYs (as in No PrEP) or is a less efficient use of resources than the combination of two other strategies (as in branded F/TAF, also called extended dominance). The ICER for CAB-LA in italics represents the comparison to generic F/TDF.

Appendix Table 7. Scenario analysis: Model-projected 10-year clinical, cost, and cost effectiveness outcomes of CAB-LA vs. population who could not effectively use oral PrEP among MSM/TGW in the US

Strategy	Total Transmissions, n	Total QALY	Incremental QALY	Total cost, billion*	Incremental cost, billion*	ICER, $/QALY*
MSM/TGW at VHR (n=476,700)						
No PrEP	178,000	4,529,000	--	33.48	--	--
CAB-LA	107,000	4,654,000	125,000	*75.84*	*42.36*	*1,553,000*
MSM/TGW at HR (n=1,906,800)						
No PrEP	197,000	16,864,000	--	39.57	--	--
CAB-LA	119,000	17,022,000	158,000	*226.32*	*186.75*	*4,614,000*

CAB-LA, long-acting injectable cabotegravir; HR, high risk for HIV; ICER, incremental cost-effectiveness ratio; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life-year; TGW, transgender women; 2020 USD, 2020 US dollars; VHR, very high risk for HIV.

* All economic outcomes are reported in 2020 US dollars. CAB-LA economic outcomes (in italics) were modeled using the upper bound drug price for CAB-LA (price $25,850).

Strategies are listed in order of increasing cost per cost-effectiveness convention, and increments are expressed compared to the next less costly strategy; the order of strategies may differ throughout the paper. Results are discounted at 3 percent per year and rounded to the nearest thousand. The ICER is the difference in cost divided by the difference in life expectancy for each strategy compared with the next less costly strategy.

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Appendix Table 8. Model-projected 10-year clinical, cost, and cost effectiveness outcomes of CAB-LA vs. generic F/TDF and branded F/TAF for HIV PrEP among MSM/TGW in the US (excluding the impact of transmissions)

Strategy	Total transmissions, n	Total QALY	Incremental QALY	Total cost, billion*	Incremental cost, billion*	ICER, $/QALY*
MSM/TGW at VHR (n = 476,700)						
No PrEP	178,000	3,966,000	--	13.82	--	--
Generic F/TDF	122,000	4,026,000	60,000	18.44	4.62	77,000
Branded F/TAF	122,000	4,028,000	2,000	45.80	27.37	Excluded
CAB-LA	107,000	4,043,000	15,000	*60.90*	*15.09*	*2,464,000*
MSM/TGW at HR (n = 1,906,800)						
No PrEP	197,000	16,238,000	--	17.72	--	--
Generic F/TDF	135,000	16,313,000	75,000	31.69	13.97	187,000
Branded F/TAF	135,000	16,321,000	8,000	144.36	112.67	Excluded
CAB-LA	119,000	16,340,000	19,000	*210.26*	*65.90*	*6,546,000*

CAB-LA, long-acting injectable cabotegravir; F/TAF, emtricitabine/tenofovir alafenamide fumarate; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HIV, human immunodeficiency virus; HR, high risk for HIV; ICER, incremental cost-effectiveness ratio;

MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life-year; TGW, transgender women; VHR, very high risk for HIV.

*All economic outcomes are reported in 2020 US dollars. CAB-LA economic outcomes (in italics) were modeled using upper bound drug price of CAB-LA (price $25,850).

Strategies are listed in order of increasing cost per cost-effectiveness convention, and increments are expressed compared to the next less costly strategy; the order of strategies may differ throughout the paper. Results are discounted at 3 percent per year and rounded to the nearest thousand. The ICER is the difference in cost divided by the difference in life expectancy for each strategy compared with the next less costly strategy. Strategies which are “Excluded” represent either a scenario where the strategy costs more and accrues fewer QALYs (as in No PrEP) or is a less efficient use of resources than the combination of two other strategies (as in branded F/TAF, also called extended dominance). The ICER for CAB-LA in italics represents the comparison to generic F/TDF.

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FIGURE LEGENDS

Appendix Figure 1. HIV incidence and primary transmission

This figure depicts the approach to modeled primary transmissions arising from the cohort of men who have sex with men and transgender women (MSM/TGW) at very high risk for HIV (VHR) for Panel **A)** No PrEP, Panel **B)** generic F/TDF and branded F/TAF, and Panel **C)** CAB-LA strategies. Black figures represent individuals who do not acquire HIV during the 10-year modeled horizon; red figures represent individuals who acquire HIV during the 10-year modeled horizon; and blue figures represent primary transmissions, individuals outside of the initial modeled cohort to whom newly diagnosed MSM/TGW will transmit. Gray figures represent possible averted HIV incident cases within the initial modeled cohort over the 10-year model horizon, as well as possible averted primary transmissions due to PrEP.

The modeled cohort is initially comprised of individuals without HIV (black figures). Over time, some of these individuals acquire HIV (red figures) with the following HIV incidence rates: off PrEP: 5.32/100PY; generic F/TDF and branded F/TAF: 1.33/100PY; CAB-LA: 0.26/100PY. Due to PrEP efficacy in reducing HIV incidence, PrEP strategies prevent incident cases (gray figures) among the initial modeled cohort over the simulation period. MSM/TGW who acquire HIV (red figures) over time will generate primary transmissions (blue figures) outside the initial modeled cohort. In the PrEP strategies, when fewer members of the primary cohort acquire HIV, primary transmissions are subsequently averted (gray figures).

The sizes of the modeled initial cohort and the incident cases were fit to scale.

Abbreviations: CAB-LA, long-acting injectable cabotegravir; F/TAF, emtricitabine/tenofovir alafenamide fumarate; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HR, high risk for HIV; MSM/TGW, men who have sex with men and transgender women**;** PrEP, pre-exposure prophylaxis; PY, person years; VHR, very high risk for HIV.

Appendix Figure 2. Annual costs reported over 10 years for MSM/TGW at **A-D)** VHR (n=476,700) and **E-H)** HR (n=1,906,800) in the US (with and without primary transmissions)

Panels depict the annual total and component costs, including annual PrEP drug, ART drug and HIV care for each strategy over 10 years. Time 1 represents the first year after model start. The vertical axis shows annual total and component costs, in billions of 2020 US dollars. The solid lines show model results for the initial cohort (n=476,700 for MSM at VHR, n=1,906,800 for MSM at HR). The dashed lines show model results inclusive of primary transmission (n=654,700 for MSM at VHR, n=2,103,800 for MSM at HR). In panels **C), D), G)** and **H)** insets magnify results to permit visualization of distinct component costs.

Abbreviations: ART, antiretroviral therapy; F/TAF, emtricitabine/tenofovir alafenamide fumarate; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HR, high risk for HIV; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; VHR, very high risk for HIV.

Appendix Figure 3. One-way sensitivity analysis: Impact of selected parameters on incremental quality-adjusted life years of CAB-LA PrEP over generic F/TDF at A) VHR (n=476,700) and B) HR (n=1,906,800)

These figures represent sensitivity analysis on a range of values for select parameters (in parentheses on vertical axis) for Panel A) VHR and Panel B) HR . The order of the values in parentheses reflects their effect on the incremental QALYs accrued by CAB-LA PrEP compared to generic F/TDF PrEP (*e.g.*, 2x base case values for HIV incidence leads to greater QALYs accrued, whereas 2x base case values for the monthly probability of being lost to follow-up leads to fewer QALYs accrued). The range of QALYs for each varied parameter is indicated by the blue horizontal bars. Longer horizontal bars indicate parameters to which the model results were more sensitive. Varying these parameters had no impact on results: acute phase duration, CD4 at infection, HIV care cost, initial PrEP uptake, integrase-based ART efficacy, return to HIV care (VHR only), lost to HIV care (HR only), and virologic failure (HR only).

Abbreviations: ART, antiretroviral therapy; CAB-LA, long-acting injectable cabotegravir; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HR: high risk for HIV; PrEP, pre-exposure prophylaxis; QALY: quality-adjusted life year; VHR, very high risk for HIV.

Appendix Figure 4. One-way sensitivity analysis: Impact of selected parameters on price premium of CAB-LA over generic F/TDF at a willingness-to-pay threshold of $100,000/QALY at **A)** VHR (n=476,700) and **B)** HR (n=1,906,800)

These figures represent sensitivity analysis on a range of values for select parameters (in parentheses on vertical axis) for Panel A) VHR and Panel B) HR. The order of these values represents their effect on the price premium at which CAB-LA would have an ICER of $100,000/QALY (dotted black vertical line) (*e.g.*, 2x base case values for HIV incidence leads to a higher price premium, whereas 2x base case values for monthly probability of being lost to follow-up leads to a lower price premium). Branded F/TAF is always dominated (*i.e.,* excluded)

297 and thus the comparator is always generic F/TDF. The first value is the one which permits a
298 higher price premium of CAB-LA, and the second would only be cost-effective at a lower price
299 premium. Price premiums of CAB-LA, given a price of $360/year for generic F/TDF, are on the
300 horizontal axis, in 2020 USD/QALY. The range of price premiums for each varied parameter is
301 indicated by the blue horizontal bars. Longer blue horizontal bars indicate parameters to which
302 the model results were more sensitive. Varying these parameters had no impact on results:
303 acute phase duration, CD4 at infection, integrase-based ART efficacy, initial PrEP uptake (VHR
304 only), initial age (VHR only), and virologic failure (HR only).
305
306 Abbreviations: ART, antiretroviral therapy; CAB-LA, long-acting injectable cabotegravir; F/TDF,
307 emtricitabine/tenofovir disoproxil fumarate; HR, high risk for HIV; ICER, incremental cost-
308 effectiveness ratio; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year; USD,
309 United States Dollar; VHR, very high risk for HIV.
310
311 **Appendix Figure 5.** Sensitivity analysis: Maximum price premiums of CAB-LA PrEP over
312 generic F/TDF at different willingness-to-pay thresholds and transmissions for MSM/TGW at
313 VHR (n=476,700) and HR (n=1,906,800) in the US over 10 years
314
315 Sensitivity analysis on transmissions and maximum price premiums of CAB-LA PrEP at different
316 willingness-to-pay thresholds. The vertical axis reports the maximum price premiums of CAB-LA
317 over generic F/TDF. The horizontal axis reports willingness-to-pay thresholds, up to
318 $300,000/QALY. For the VHR cohort, in the absence of PrEP, primary transmissions range from
319 20,000-197,000 (7%-70% of all transmissions from MSM/TGW). Primary transmissions for VHR
320 are shown in the solid lines (red: 70% transmission; purple: 63% transmission; green: 35%
321 transmission; blue: 7% transmission). For HR, primary transmissions range from 28,200-

282,000 (10%-100% of all transmissions arising from MSM/TGW). Primary transmissions for HR are shown in the dashed lines (red: 100% transmission; purple: 70% transmission; green: 50% transmission; blue: 10% transmission).

Abbreviations: CAB-LA, long-acting injectable cabotegravir; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HR, high risk for HIV; MSM/TGW, men who have sex with men / transgender women; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life-year; VHR, very high risk for HIV.

Appendix Figure 6. Annual costs reported over 10 years for MSM/TGW at HR in the US (n=1,906,800)

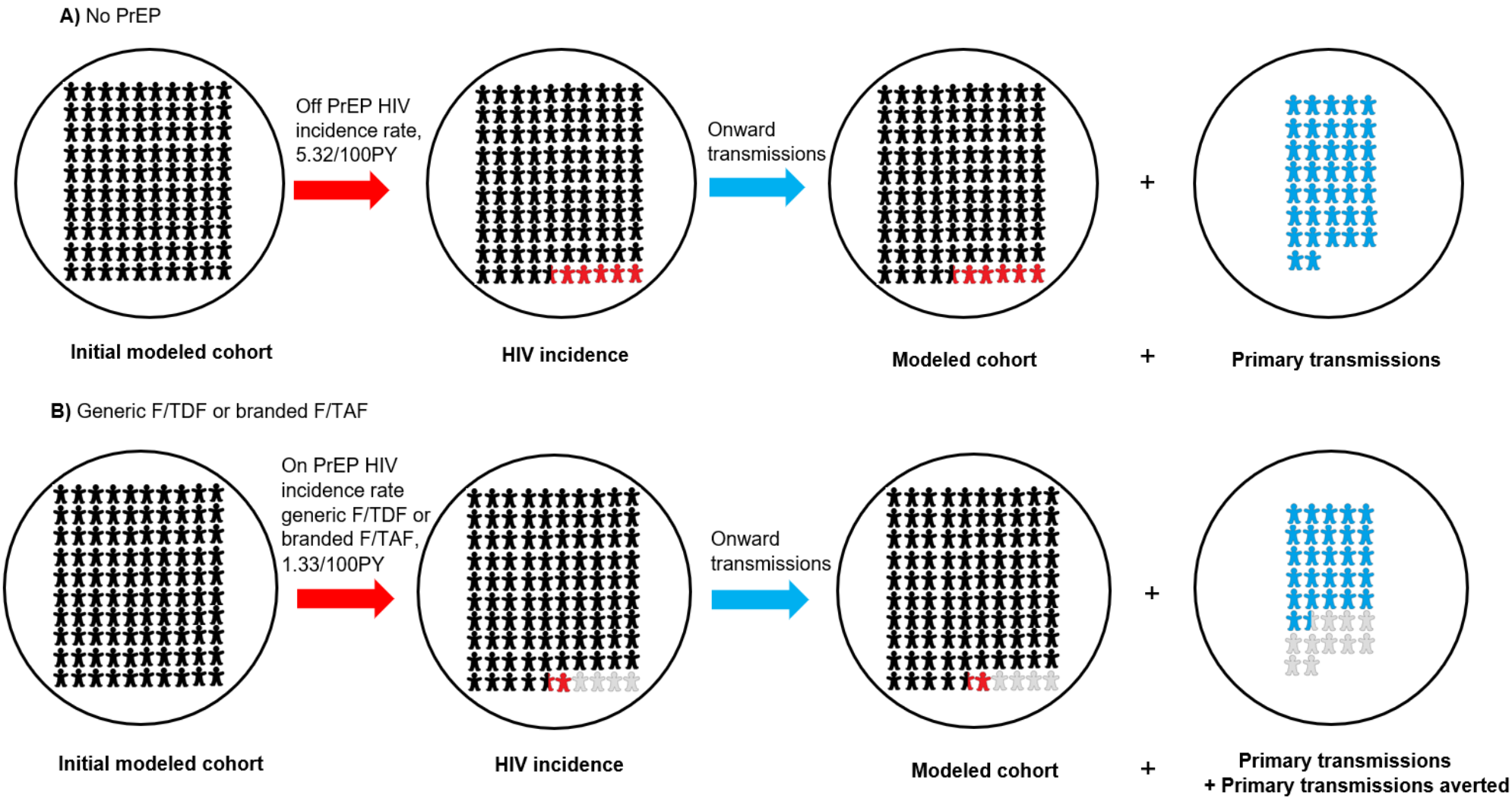
Panels depict the projected total annual component costs for each PrEP strategy for the HR population (Panel A: No PrEP; Panel B: generic F/TDF; Panel C: branded F/TAF; and Panel D: CAB-LA). Time 1 on the horizontal axis represents the first year since the start of the model simulation. The left vertical axis shows annual total cost in billion (B) 2020 US dollars. Annual component costs are given by the solid colors (ART drug: dark purple; HIV care: light purple; PrEP drug: dark blue; PrEP program: light blue) at any given timepoint in the model simulation period (horizontal axis). For example, during Year 5 in Panel B, total annual cost was $3.33B ($2.33B, HIV care: $381.57 million (M), PrEP drug: $231.07M, PrEP program: $385.84M).

Abbreviations: ART, antiretroviral therapy; CAB-LA, long-acting injectable cabotegravir; F/TAF, emtricitabine/tenofovir alafenamide fumarate; F/TDF, emtricitabine/tenofovir disoproxil fumarate;

346 HR: High risk for HIV; MSM/TGW, men who have sex with men / transgender women; PrEP,

347 pre-exposure prophylaxis.

Appendix Figure 1. HIV incidence and transmission



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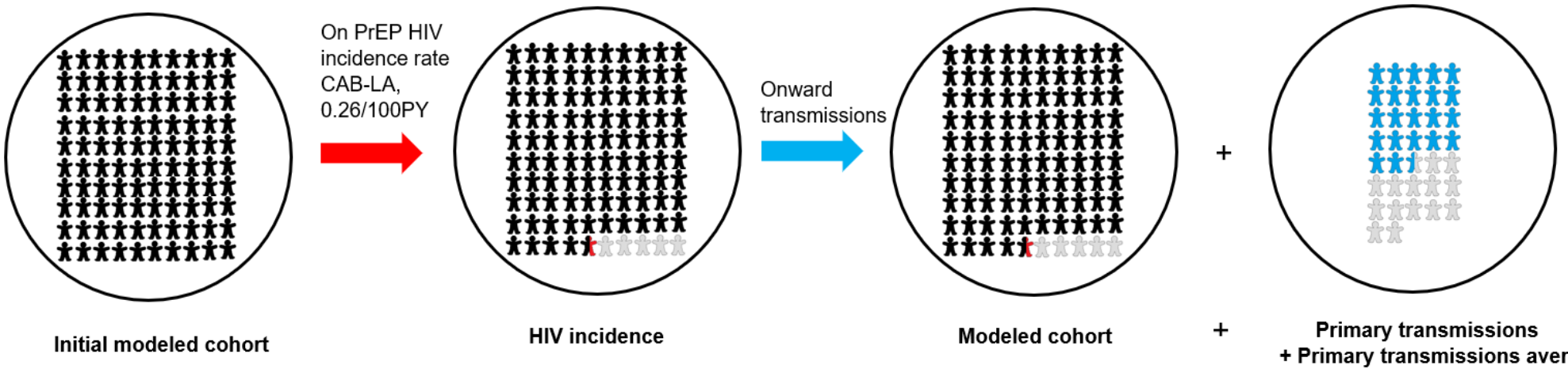
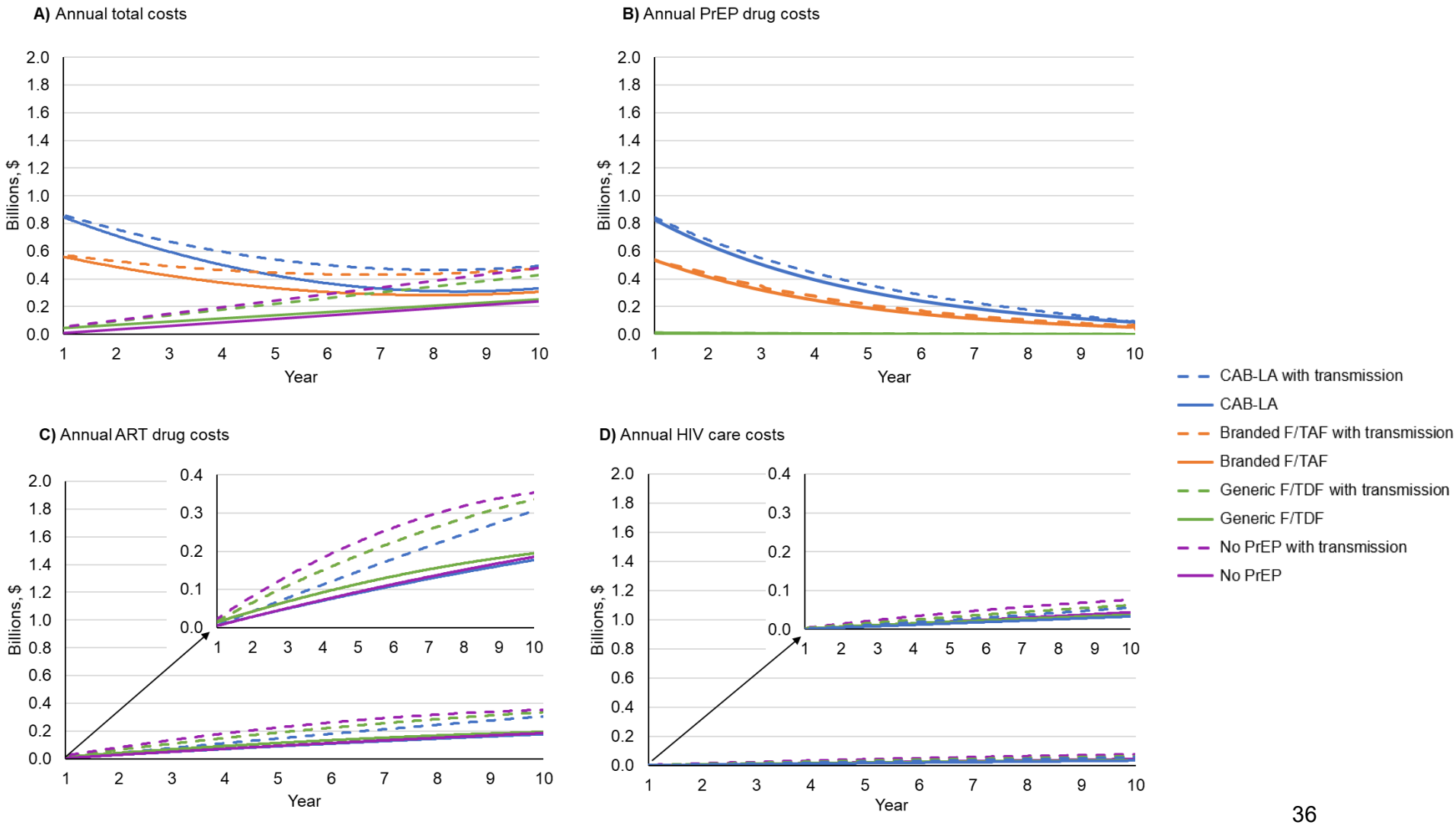
C) CAB-LA



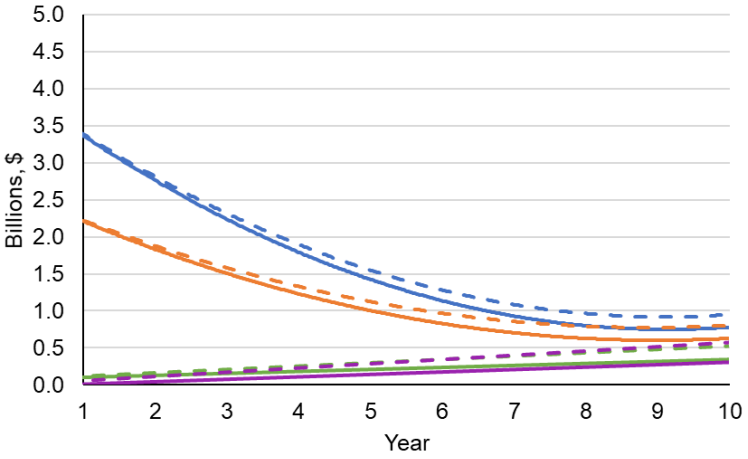
Legend

- People without HIV
- HIV incidence
- HIV incident cases averted or primary transmissions averted
- Primary transmissions

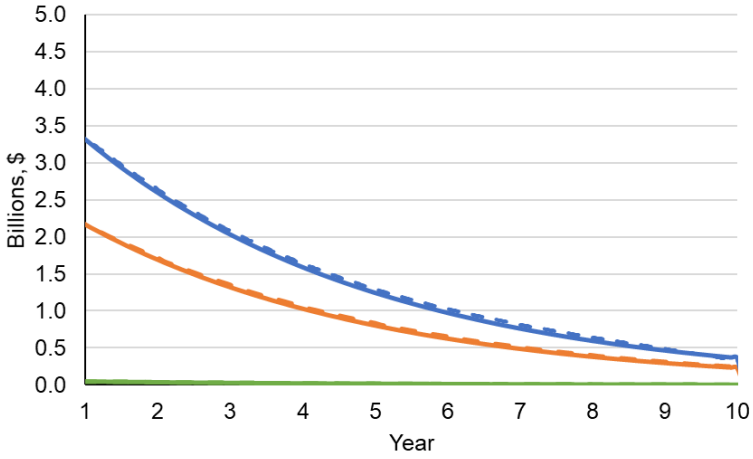
Appendix Figure 2. Annual costs reported over 10 years for MSM/TGW at **A-D)** VHR (n=476,700) and **E-H)** HR (n=1,906,800) in the US (with and without primary transmissions)



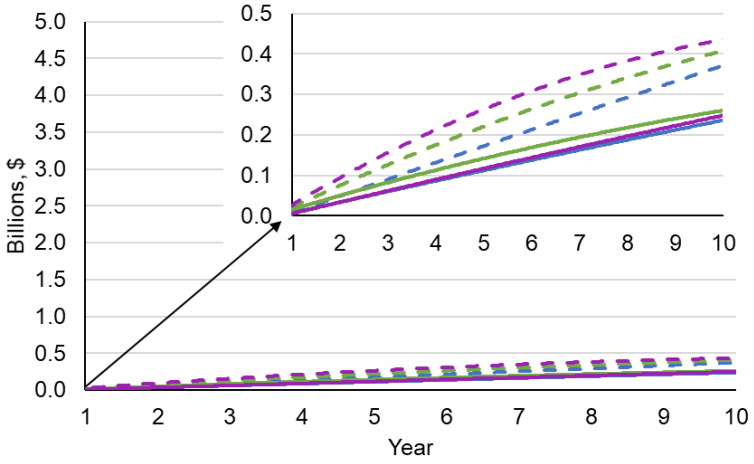
E) Annual total costs



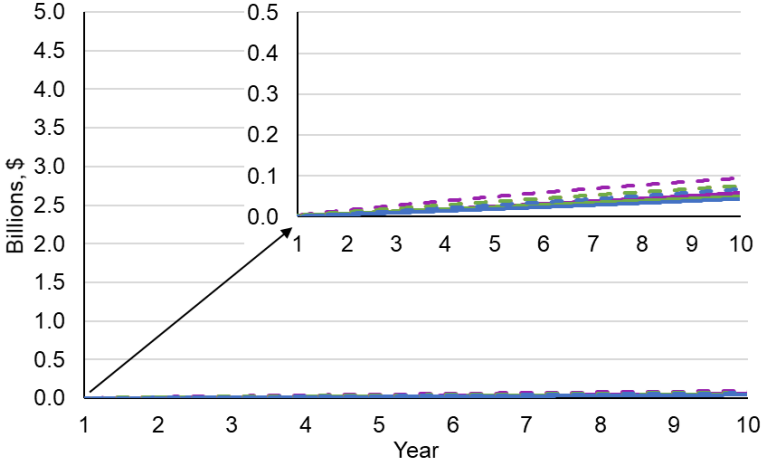
F) Annual PrEP drug costs



G) Annual ART drug costs



H) Annual HIV care costs

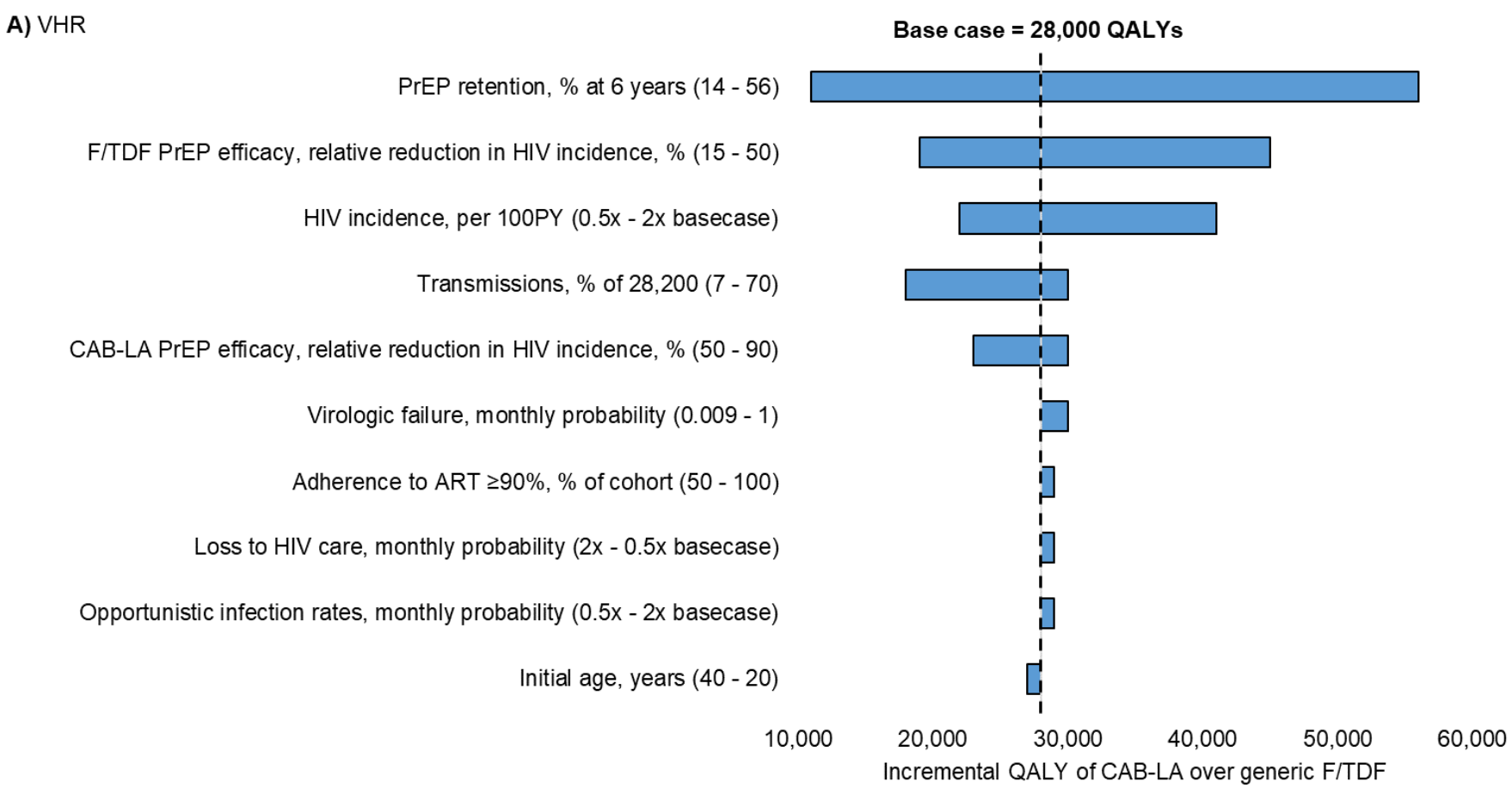


353

354 **Appendix Figure 3**. One-way sensitivity analysis: Impact of selected parameters on incremental quality-adjusted life years of CAB-

355 LA PrEP over generic F/TDF at **A)** VHR (n=476,700) and **B)** HR (n=1,906,800)

356



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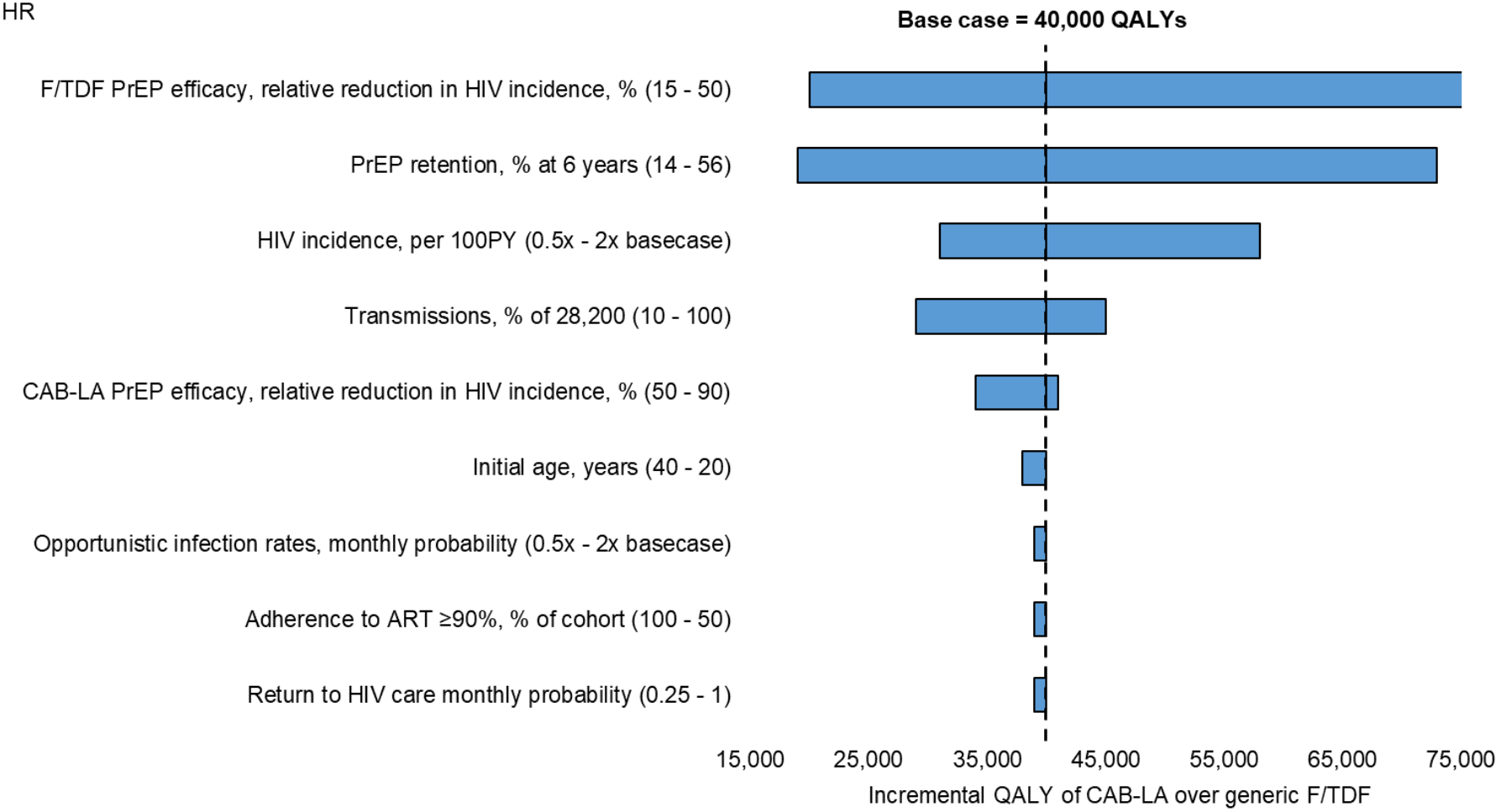
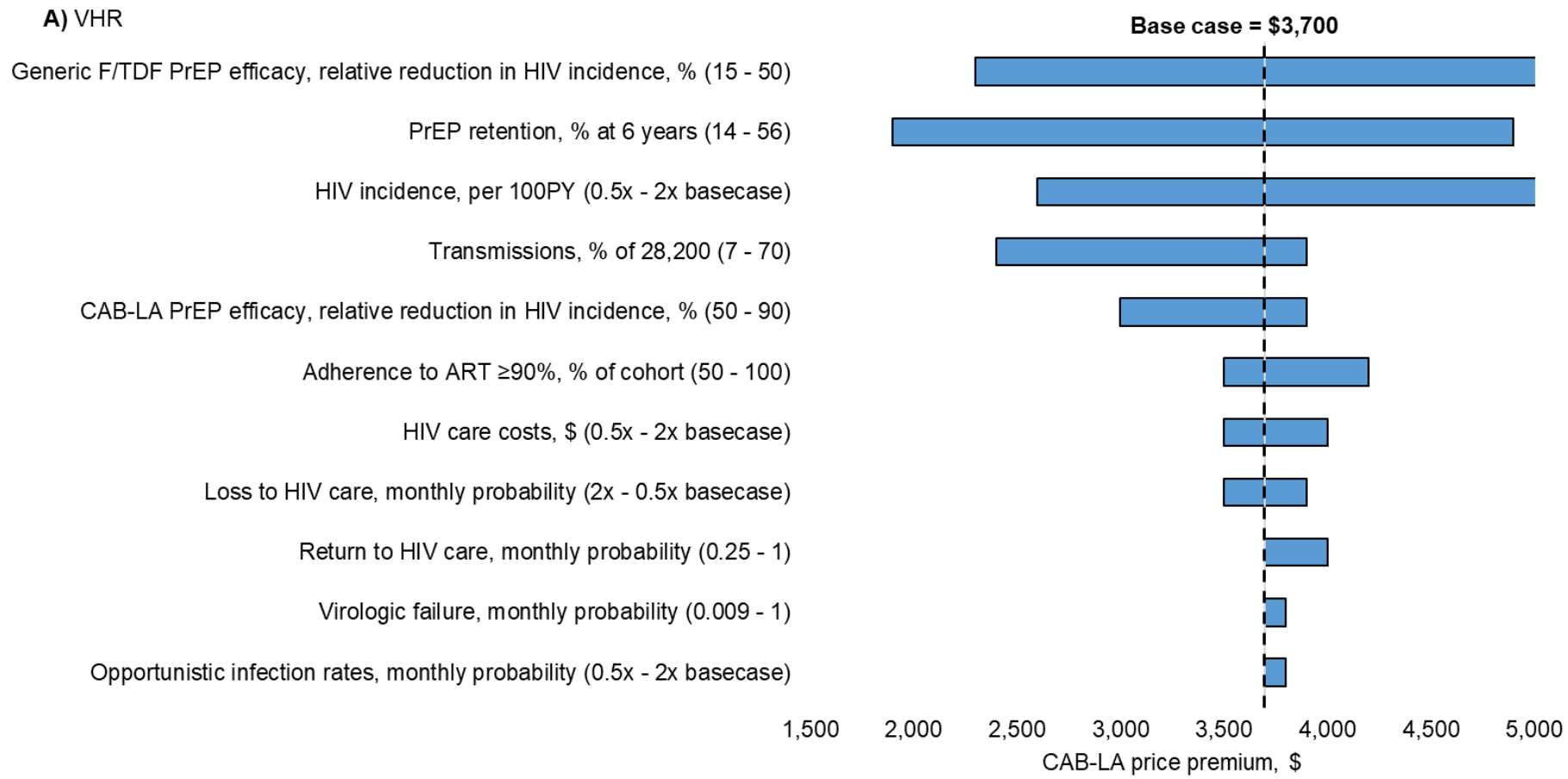
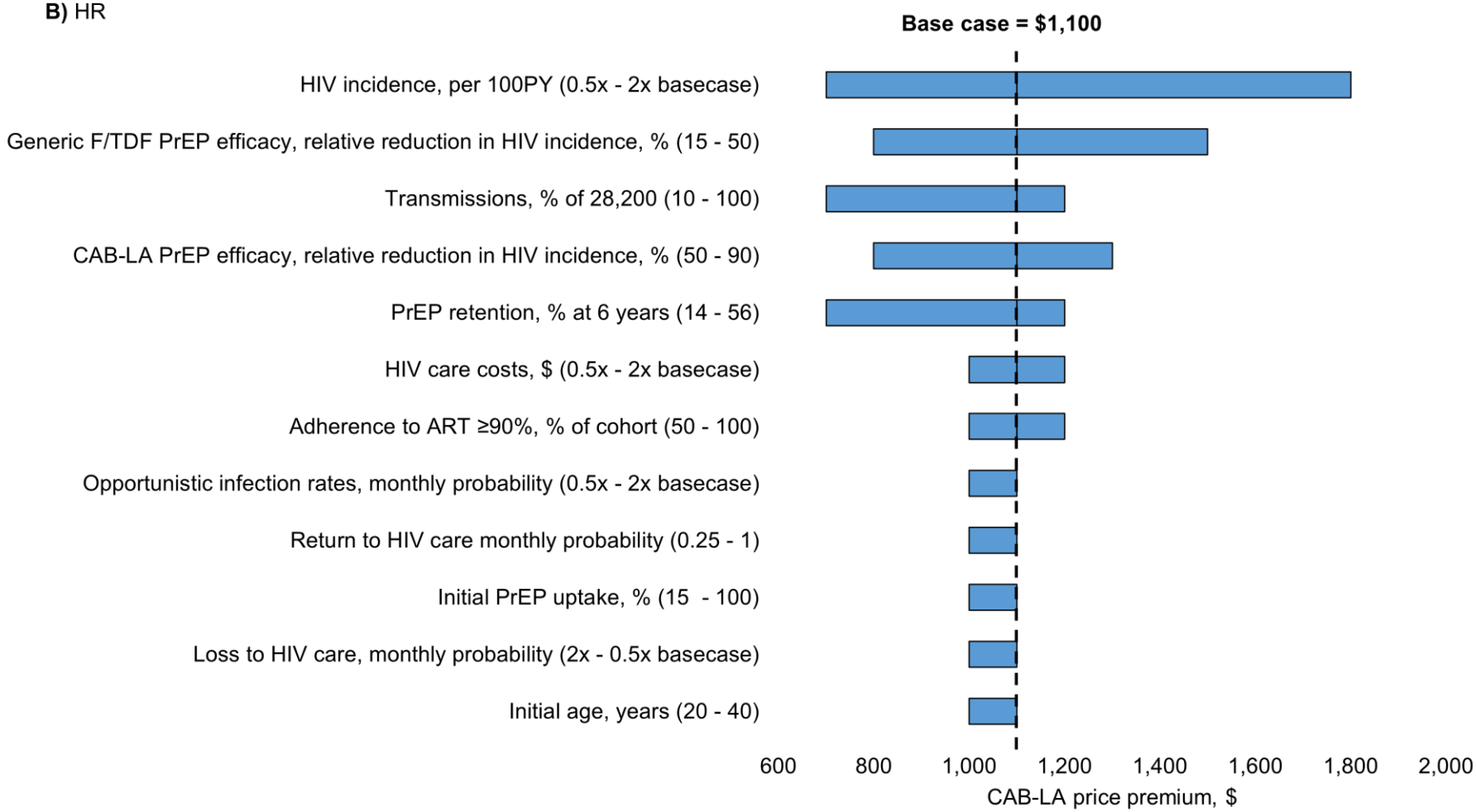
B) HR


Base case = 40,000 QALYs
F/TDF PrEP efficacy, relative reduction in HIV incidence, % (15 - 50)
PrEP retention, % at 6 years (14 - 56)
HIV incidence, per 100PY (0.5x - 2x basecase)
Transmissions, % of 28,200 (10 - 100)
CAB-LA PrEP efficacy, relative reduction in HIV incidence, % (50 - 90)
Initial age, years (40 - 20)
Opportunistic infection rates, monthly probability (0.5x - 2x basecase)
Adherence to ART ≥90%, % of cohort (100 - 50)
Return to HIV care monthly probability (0.25 - 1)
15,000
25,000
35,000
45,000
55,000
65,000
75,000
Incremental QALY of CAB-LA over generic F/TDF

Appendix Figure 4. One-way sensitivity analysis: Impact of selected parameters on price premium of CAB-LA over generic F/TDF at a willingness-to-pay threshold of $100,000/QALY at **A)** VHR (n=476,700) and **B)** HR (n=1,906,800)

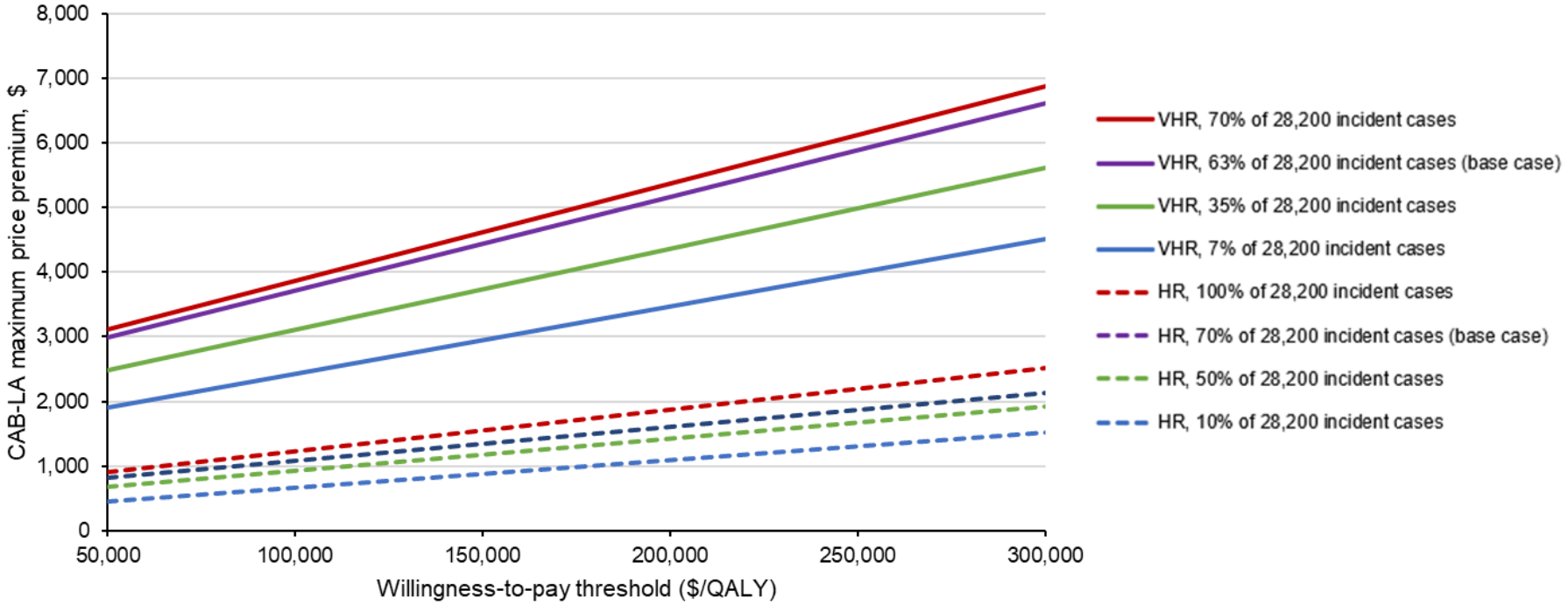


B) HR

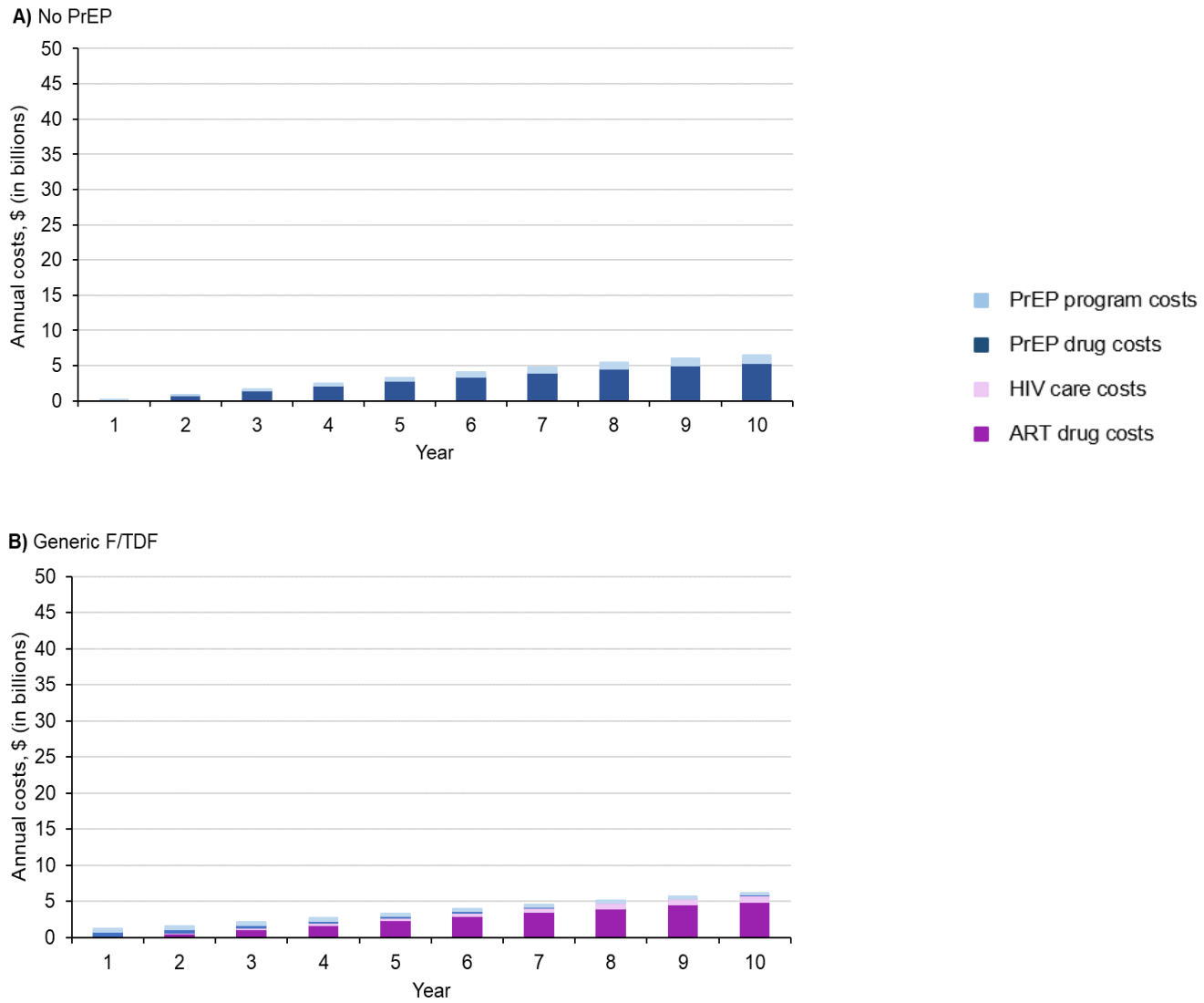

Base case = $1,100
HIV incidence, per 100PY (0.5x - 2x basecase)
Generic F/TDF PrEP efficacy, relative reduction in HIV incidence, % (15 - 50)
Transmissions, % of 28,200 (10 - 100)
CAB-LA PrEP efficacy, relative reduction in HIV incidence, % (50 - 90)
PrEP retention, % at 6 years (14 - 56)
HIV care costs, $ (0.5x - 2x basecase)
Adherence to ART ≥90%, % of cohort (50 - 100)
Opportunistic infection rates, monthly probability (0.5x - 2x basecase)
Return to HIV care monthly probability (0.25 - 1)
Initial PrEP uptake, % (15 - 100)
Loss to HIV care, monthly probability (2x - 0.5x basecase)
Initial age, years (20 - 40)
600
800
1,000
1,200
1,400
1,600
1,800
2,000
CAB-LA price premium, $

361

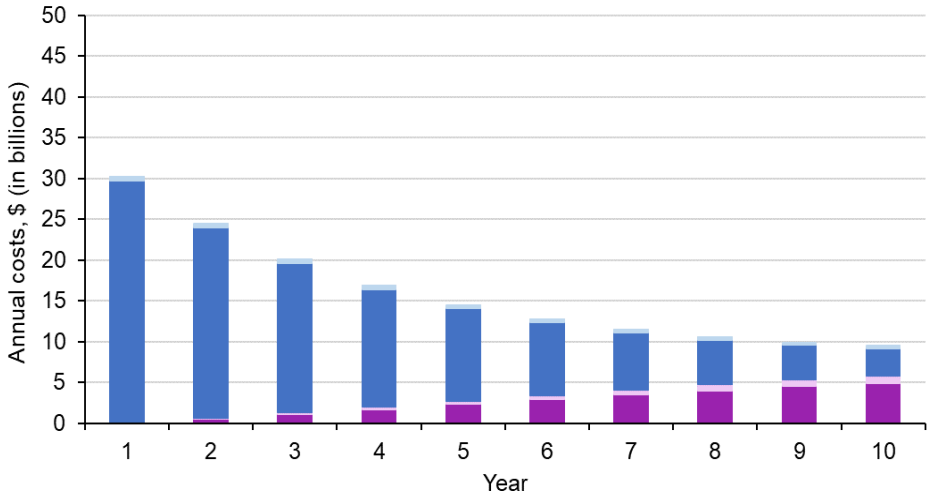
Appendix Figure 5. Sensitivity analysis: Maximum price premiums of CAB-LA PrEP over generic F/TDF at different willingness-to-pay thresholds and transmissions for MSM/TGW at VHR (n=476,700) and HR (n=1,906,800) in the US over 10 years



Appendix Figure 6. Annual costs reported over 10 years for MSM/TGW at HR in the US (n=1,906,800)



C) Branded F/TAF



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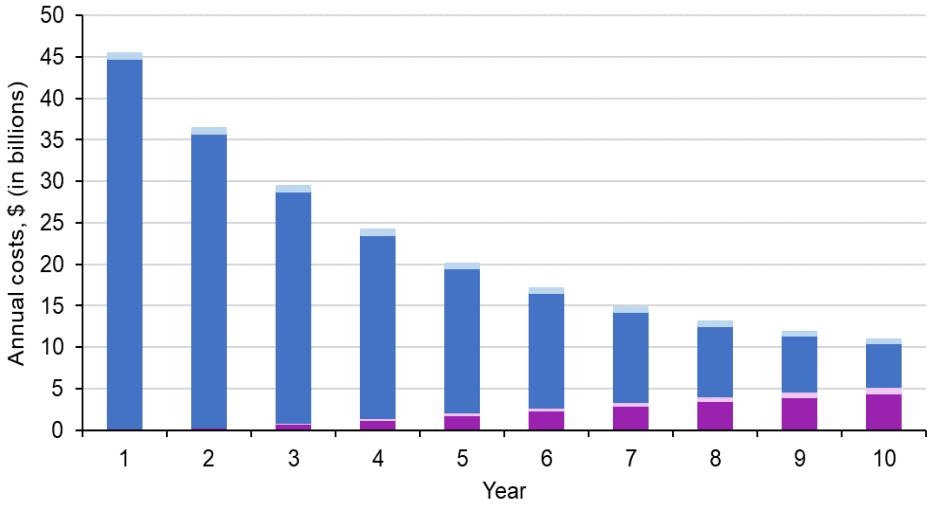
D) CAB-LA



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