SUPPLEMENTARY APPENDIX

Ending the HIV epidemic among persons who inject drugs: a cost-effectiveness analysis in six U.S. cities

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1. Cost-Effectiveness Analysis & Results

Complete cost-effectiveness results for individual interventions and for the combination implementation strategies on the production function for each city in the optimistic scenario are presented in **Supplemental Tables 1 and Supplemental Figure 1**.

2. Sensitivity Analysis

2.1 Changing opioid epidemic mortality details

Within each city, we implemented an increased risk of mortality for PWID who were not receiving medication for opioid use disorders (MOUD). We derived the elevated risk of mortality among PWID from estimates in British Columbia, Canada where fentanyl saturation in the illicit drug supply is among the highest in North America [1]. We adjusted mortality estimates for each city using state-level evidence of fentanyl prevalence: 0-1.00 encounters per 100,000 residents in California (LA); 1.01-5.00 in Florida (Miami); 0-1.00 in Georgia (Atlanta); 5.01-10.00 in Maryland (Baltimore); 1.01-5.00 in New York (NYC); 0-1.00 in Washington (Seattle) [2]. In comparison, the highest prevalence states of Massachusetts and New Hampshire reported over 20 encounters per 100,000 residents [2]. We assumed that the elevated mortality risk in British Columbia represented the mortality risk in the highest prevalence states, and adjusted rates downward for other cities accordingly. Fentanyl prevalence was only reported in ranges; therefore, we used high, midpoint and low estimates for each city. Full results are presented in **Supplemental Figures 2 & 3.**

	Increased Mortality Risk†		
	Midpoint	Low	High
Atlanta	1.02	1.00	1.03
Baltimore	1.23	1.16	1.31
Los Angeles	1.02	1.00	1.03
Miami	1.09	1.03	1.16
New York	1.09	1.03	1.16
Seattle	1.02	1.00	1.03

† Increased mortality risk adjusted down from 1.625[1] according to state-level fentanyl saturation[2]

2.2 Free PrEP details

We conducted deterministic sensitivity analysis on our results under the assumption of free PrEP provision (i.e. zero PrEP medication costs), in response to the announcement by Gilead Sciences of free PrEP provision for 200,000 HIV-negative individuals for five years [3]. Despite this donation, questions remain as to whether it will close the treatment gap for the people most in

need, relative to allowing generic manufacturing and provision of PrEP [4]. We retained implementation and sustainment costs for PrEP scale-up, as the donation of PrEP was assumed to only cover the direct costs of medication, and not overhead, labour, or other costs related to PrEP delivery. Full results are presented in **Supplemental Figures 4 & 5.**

3. Additional information

We have published elsewhere the description of the model, the evidence synthesis and the estimation of status quo service levels, the ranges for the scale-up and costs attributable to each intervention (including costs of implementation, delivery and sustainment, when applicable) and modeling assumptions for all interventions included in our study [5-10]. For simplicity, we provide some of these details for the HIV prevention programs hereafter (cost information can be found in **Supplemental Table 2**). Interventions excluded from combinations are presented in **Supplemental Figure 6**.

Conforming to best practice guidelines on cost-effectiveness analyses [11], **Supplemental Tables 3 and 4** report the Impact Inventory and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.

3.1 Syringe Service Programs

In the model, expanded access to sterile injection equipment provided by SSP reduces the number of shared injections by 58% (95% CI: 19%, 78%). [12] We note that the probability of transmission is reduced by 50% when the HIV-infected sharing partner is on ART or when the HIV-uninfected partner in on PrEP [9].

Status quo volume of syringes distributed from syringe service programs (SSP) varied greatly across city (from 5,185 per 1,000 PWID in ATL to 204,404 per 1,000 PWID in SEA) [6], and we assumed that syringes were distributed proportionally across PWID ethnic groups. We identified the best available evidence for Atlanta based on estimates from the Atlanta Harm Reduction Coalition in 2016 [13]. Estimates for Baltimore were based on the City of Baltimore Syringe Exchange Program in 2016 [14]. Estimates for Los Angeles were based on direct correspondence with the City of Los Angeles AIDS Coordinator's Office for Los Angeles [15]. Estimates for Miami were based on national CDC estimates, as local surveillance estimates were not available [16]. Estimates for New York City were based on New York state department of health reports in 2012 [17]. Estimates for Seattle were based on direct correspondence with Public Health – Seattle & King County for Seattle [18].

The optimistic scenario was defined according to WHO guidelines on good coverage for PWID and allowed for 200 syringes/PWID/year [19]. Since status quo coverage levels for Seattle are already equivalent to this scenario, we assumed 400 syringes/PWID/year.

Costs per syringe were derived from a CDC-led study and included the costs attributable to syringes as well as overhead and personnel costs while implementation costs consisted of start-up costs [20].

3.2 Medication for opioid use disorder

Access to MOUD for the 73% of PWID estimated to have an opioid use disorder [21] reduced the number of shared injections by 54% (95% CI: 33%, 68%) resulting in a reduced probability of HIV acquisition [22]. In addition, given the protective effect of MOUD in reducing overdose and other injected-related risk of death [23], PWID receiving MOUD had a reduced risk of mortality (66%; 95% CI: 48%, 78%) [23] and an increased quality of life (6%; 95% CI: 0%, 13%) [24]. Finally, MOUD also decreased the probability of ART discontinuation (34%; 95% CI: 11%, 51%) [25].

As practical considerations will often determine medication selection (e.g., access to opioid treatment programs for treatment with methadone or insurance coverage for buprenorphine) [26], we considered evidence specific to each medication. To derive status quo service levels for PWID receiving buprenorphine, we estimated DATA-waivered physician capacity accepting Medicaid for each city [6]. Estimates for receipt of methadone were derived from state-level data stratified by gender and race/ethnicity available from the Substance Abuse and Mental Health Services Administration (SAMHSA), and we adjusted for the state's proportion of opioid treatment programs situated within each city's boundaries [6].

The range for the rate of expanded access was derived using evidence of the annual rate of increase between 2011-2014 in city-level PWID receiving opioid treatment program-based MOUD with methadone from SAMHSA's latest complete Treatment Episode Data Set (TEDS) [6, 27]. The optimistic rate of expanded access was derived from the annual growth rate (16.7%) in Seattle (from 930 to 1,714).

The optimistic scenario for expanded access to office-based MOUD with buprenorphine for PWID was defined according to WHO guidelines on good coverage for PWID [19], and given the more limited expansion capacity of treatment with methadone in opioid treatment programs [28], we assumed 40% coverage of treatment with buprenorphine among PWID with an OUD.

Costs for MOUD included medication, toxicology and overhead costs, as well as intervention-specific implementation costs unique to each treatment, including physician detailing costs for office-based buprenorphine expansion, and clinic-level training/process improvement for opioid treatment program-based methadone expansion [7].

3.3 Pre-exposure prophylaxis

Expanded access to daily PrEP for all PWID resulted in a reduced probability of HIV infection via sexual contact and shared injection equipment of 60% (95% CI: 56%, 62%) [6]. We derived population-level average PrEP effectiveness by multiplying the efficacy of taking four doses per week (96%; 95% CI: 90%, 99%) [29] by the percentage of individuals that had PrEP adherence equivalent to four doses per week (62.5%) in a cohort study evaluating adherence when PrEP was provided free of charge in community-based clinics [30]. We assumed that individuals on PrEP were tested for HIV every 3 months, as per CDC guidelines [31].

Given the paucity of evidence on PrEP uptake among PWID, we assumed no PrEP among PWID in the status quo and that expanded access in the optimistic scenarios would result in a coverage level of 50%.

Costs for PrEP included medication costs (accounting for financial support provided by the Gilead Advancing Access program), HIV testing costs and time for physician consultations [7, 32]. Implementation costs included provider outreach and detailing to increase physician capacity for the prescription of PrEP [7].

ATLANTA

Supplement Table 1. Panel A. Results of incremental cost-effectiveness analysis for combination implementation strategies comprising Atlanta's health production function

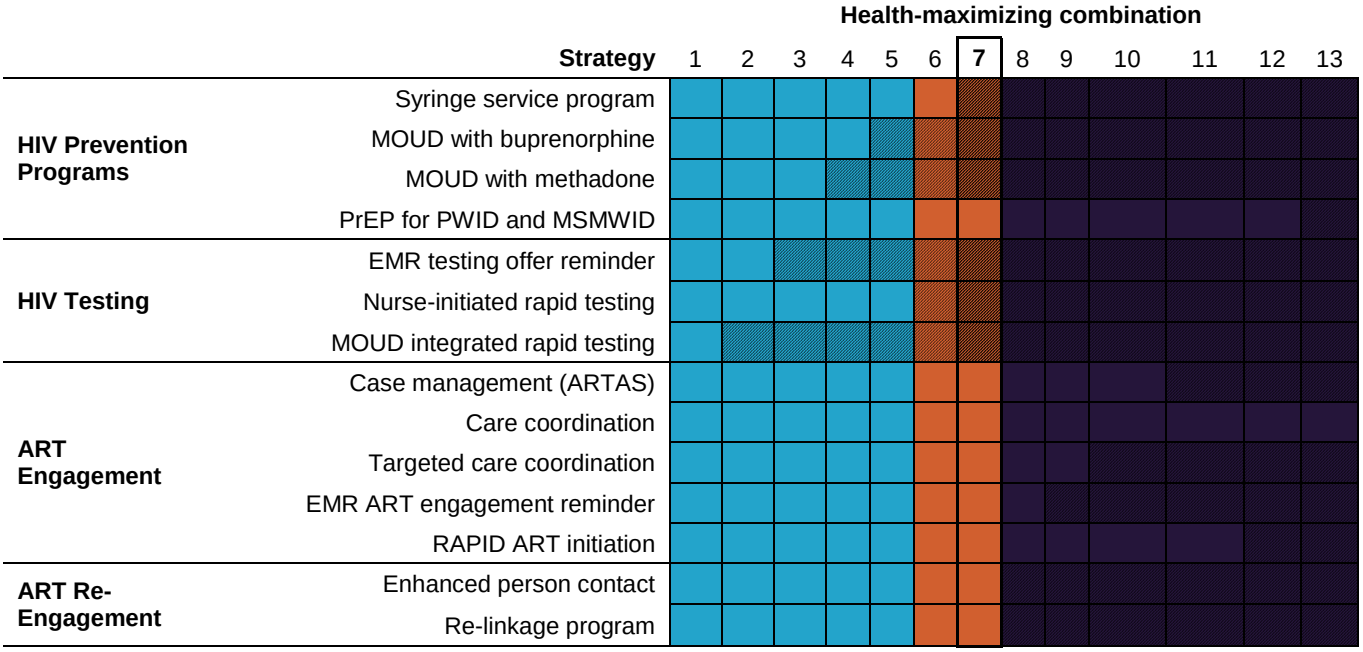
Atlanta

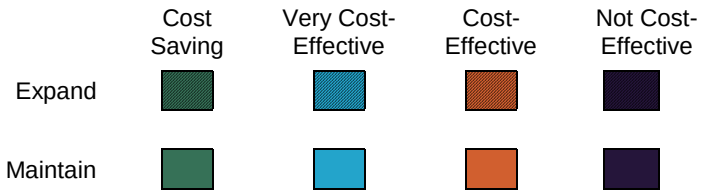
Strategy	*Incremental Cost: $M*	*Incremental QALYs*	*ICER: $ / QALY*
1	0.0	0	-
2	0.1	23	4,649
3	6.6	381	18,224
4	7.1	396	28,670
5	464.6	15,627	30,039
6	477.3	15,803	72,056
7	**503.3**	**16,013**	**124,165**
8	545.3	16,257	171,961
9	586.5	16,484	181,576
10	590.1	16,497	266,883
11	606.2	16,549	313,350
12	609.5	16,555	573,045
13	2834.6	17,051	4,482,135

$B: billions of $US; $M: millions of $US (both in 2018 $US); QALYs: quality-adjusted life years; ICER: incremental cost-effectiveness ratio; CS: cost-saving. Each of the strategies 1 through 10 represent the highest-valued strategies for a given investment level. Incremental costs and QALYs are compared against the next-most-costly strategy on the production function (i.e. Strategy 2 versus 1, 3 versus 2 etc.).

ATLANTA

Supplement Table 1. Panel B. Combination implementation strategies, delivered at optimistic implementation scale-up, residing on Atlanta's health production function





QALY – Quality adjusted life year; ICER – Incremental cost-effectiveness ratio; MOUD – Medication for opioid use disorder; PrEP – Pre-exposure prophylaxis; MSM – men who have sex with men; EMR – Electronic medical record; ARTAS – Anti-Retroviral Treatment and Access to Services; ART – Antiretroviral therapy; RAPID – Rapid ART Program for Individuals with an HIV Diagnosis.

† The health-maximizing strategy that remained cost-effective was determined by calculating the incremental cost-effectiveness ratio, defined as the additional cost of a specific combination implementation strategy divided by its additional health benefit, as compared with the next-most-costly strategy on the health production function. Combination implementation strategies with ICERs less than $50,000/QALY were considered very cost-effective, while those with ICERs < $150,000/QALY were considered cost-effective. The numerator represents the total increment in healthcare costs (in 2018 US$) for the adult population (aged 15-64) in a given city, and the denominator represents the total gain in quality-adjusted life years for this group.

ATLANTA

Supplement Table 1. Panel C. Incremental costs, QALYs and incremental cost-effectiveness ratios (ICER) of individual interventions

Intervention	Atlanta		
HIV prevention programs	*ΔTC ($M)*	*ΔQALYs*	*ICER ($'000s)*
Syringe service program	12.2 [-372.6 - 146.6]	320 [-186 - 1731]	38.1 [CS - 1460.7]
MOUD with buprenorphine	458.2 [211.7 - 1114.7]	15152 [10374 - 20390]	30.2 [13.8 - 81.7]
MOUD with methadone	0.4 [-140.6 - 136.1]	15 [-493 - 561]	28.6 [CS - 218.6]
PrEP for PWID and MSMWID	2175.6 [1458.6 - 2606.7]	825 [308 - 3508]	2636.1 [409.1 - 5988.9]
HIV Testing			
EMR testing offer reminder	6.5 [-162.3 - 134.6]	363 [-58 - 1522]	18.0 [CS - 1190.1]
Nurse-initiated rapid testing	11.0 [-150.8 - 138.4]	267 [-131 - 1389]	41.4 [CS - 1367.9]
MOUD integrated rapid testing	0.1 [-141.6 - 134.8]	23 [-480 - 581]	4.6 [CS - 376.9]
ART engagement			
Case management (ARTAS)	15.3 [-118.9 - 161.8]	46 [-452 - 605]	334.9 [CS - 2180.1]
Care coordination	19.2 [-117.3 - 161.8]	20 [-482 - 568]	952.3 [CS - 1253.4]
Targeted care coordination	3.8 [-135.9 - 139.1]	16 [-486 - 565]	231.8 [CS - 351.4]
EMR ART engagement reminder	43.5 [-106.4 - 183.5]	250 [-251 - 871]	174.5 [CS - 2209.5]
RAPID ART initiation	3.7 [-136.0 - 139.7]	7 [-496 - 561]	555.4 [CS - 295.0]
ART re-engagement			
Enhanced personal contact	27.0 [-114.3 - 163.0]	158 [-337 - 749]	171.5 [CS - 2061.2]
Re-linkage program	16.9 [-127.6 - 154.1]	101 [-388 - 684]	167.0 [CS - 1826.7]

* Values represent the results obtained from the deterministic analysis and the 95% credible interval in brackets from the probabilistic sensitivity analysis over 2,000 simulations.
QALY: Quality-adjusted life years; TC: Total costs; CS: Cost-saving; PWID: People who inject drugs; MSM: Men who have sex with men; PrEP: Pre-exposure prophylaxis; MOUD: Medication for opioid use disorder; ART: Antiretroviral therapy; EMR: Electronic medical records; RAPID: Rapid ART Program for Individuals with an HIV Diagnosis.

BALTIMORE

Supplement Table 1. Panel A. Results of incremental cost-effectiveness analysis for combination implementation strategies comprising Baltimore's health production function

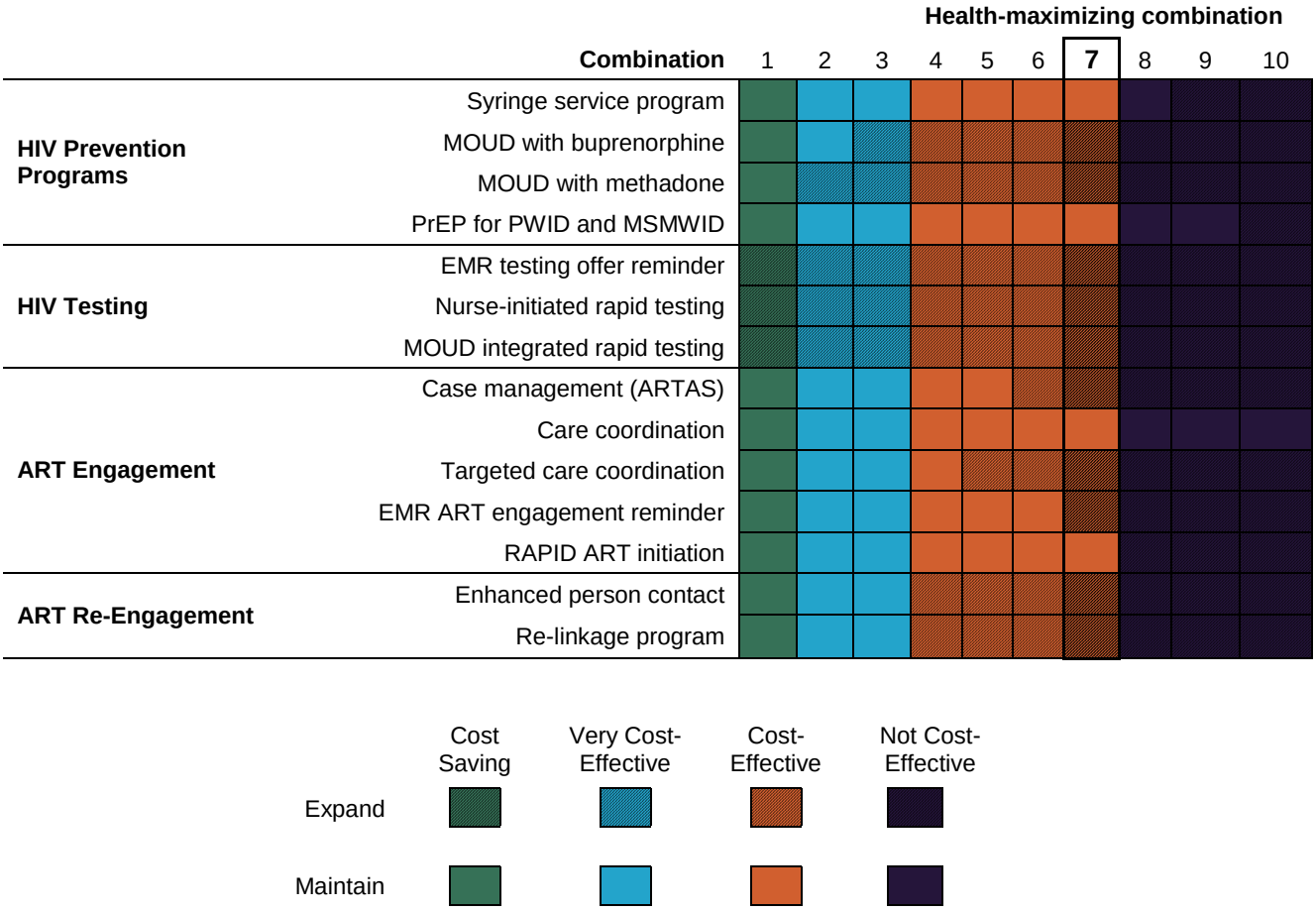
Baltimore

Strategy	*Incremental Cost: $M*	*Incremental QALYs*	*ICER: $ / QALY*
1	-9.4	331	CS
2	14.2	902	41,378
3	474.1	10,442	48,201
4	507.2	10,711	123,123
5	512.3	10,752	125,340
6	515.3	10,775	133,011
7	**555.5**	**11,075**	**133,625**
8	556.7	11,083	164,865
9	653.8	11,171	1,097,114
10	3135.6	11,667	5,010,583

$B: billions of $US; $M: millions of $US (both in 2018 $US); QALYs: quality-adjusted life years; ICER: incremental cost-effectiveness ratio; CS: cost-saving. Each of the strategies 1 through 8 represent the highest-valued strategies for a given investment level. Incremental costs and QALYs are compared against the next-most-costly strategy on the production function (i.e. Strategy 2 versus 1, 3 versus 2 etc.).

BALTIMORE

Supplement Table 1. Panel B. Combination implementation strategies, delivered at optimistic implementation scale-up, residing on Baltimore's health production function



QALY – Quality adjusted life year; ICER – Incremental cost-effectiveness ratio; MOUD – Medication for opioid use disorder; PrEP – Pre-exposure prophylaxis; MSM – men who have sex with men; EMR – Electronic medical record; ARTAS – Anti-Retroviral Treatment and Access to Services; ART – Antiretroviral therapy; RAPID – Rapid ART Program for Individuals with an HIV Diagnosis.

† The health-maximizing strategy that remained cost-effective was determined by calculating the incremental cost-effectiveness ratio, defined as the additional cost of a specific combination implementation strategy divided by its additional health benefit, as compared with the next-most-costly strategy on the health production function. Combination implementation strategies with ICERs less than $50,000/QALY were considered very cost-effective, while those with ICERs < $150,000/QALY were considered cost-effective. The numerator represents the total increment in healthcare costs (in 2018 US$) for the adult population (aged 15-64) in a given city, and the denominator represents the total gain in quality-adjusted life years for this group.

BALTIMORE

Supplement Table 1. Panel C. Incremental costs, QALYs and incremental cost-effectiveness ratios (ICER) of individual interventions

Intervention	Baltimore		
HIV prevention programs	*ΔTC ($M)*	*ΔQALYs*	*ICER ($'000s)*
Syringe service program	96.2 [-5.8 - 203.0]	126 [-257 - 495]	762.7 [CS - 4918.6]
MOUD with buprenorphine	462.6 [285.9 - 1140.4]	9457 [5248 - 14281]	48.9 [29.1 - 147.7]
MOUD with methadone	23.7 [-64.2 - 138.3]	570 [165 - 1030]	41.6 [CS - 666.4]
PrEP for PWID and MSMWID	2474.9 [2036.7 - 3018.6]	632 [119 - 918]	3917.3 [2421.1 - 8783.6]
HIV Testing			
EMR testing offer reminder	-4.6 [-101.4 - 101.8]	169 [-216 - 496]	CS [CS - 2153.4]
Nurse-initiated rapid testing	-5.0 [-103.7 - 98.4]	164 [-204 - 518]	CS [CS - 1782.7]
MOUD integrated rapid testing	-0.5 [-97.7 - 103.9]	22 [-347 - 361]	CS [CS - 238.2]
ART engagement			
Case management (ARTAS)	3.0 [-92.8 - 108.4]	19 [-351 - 354]	159.4 [CS - 506.2]
Care coordination	17.6 [-75.5 - 126.0]	40 [-336 - 376]	437.8 [CS - 2176.1]
Targeted care coordination	5.5 [-91.5 - 110.5]	44 [-326 - 385]	123.3 [CS - 1111.1]
EMR ART engagement reminder	45.2 [-59.3 - 149.5]	339 [-117 - 710]	133.2 [CS - 1790.8]
RAPID ART initiation	1.3 [-95.9 - 106.0]	7 [-363 - 341]	187.2 [CS - 52.1]
ART re-engagement			
Enhanced personal contact	21.7 [-77.2 - 125.6]	173 [-230 - 526]	125.3 [CS - 2520.2]
Re-linkage program	13.9 [-83.0 - 117.6]	111 [-260 - 464]	125.0 [CS - 2064.8]

* Values represent the results obtained from the deterministic analysis and the 95% credible interval in brackets from the probabilistic sensitivity analysis over 2,000 simulations.
QALY: Quality-adjusted life years; TC: Total costs; CS: Cost-saving; PWID: People who inject drugs; MSM: Men who have sex with men; PrEP: Pre-exposure prophylaxis; MOUD: Medication for opioid use disorder; ART: Antiretroviral therapy; EMR: Electronic medical records; RAPID: Rapid ART Program for Individuals with an HIV Diagnosis.

LOS ANGELES

Supplement Table 1. Panel A. Results of incremental cost-effectiveness analysis for combination implementation strategies comprising Los Angeles's health production function

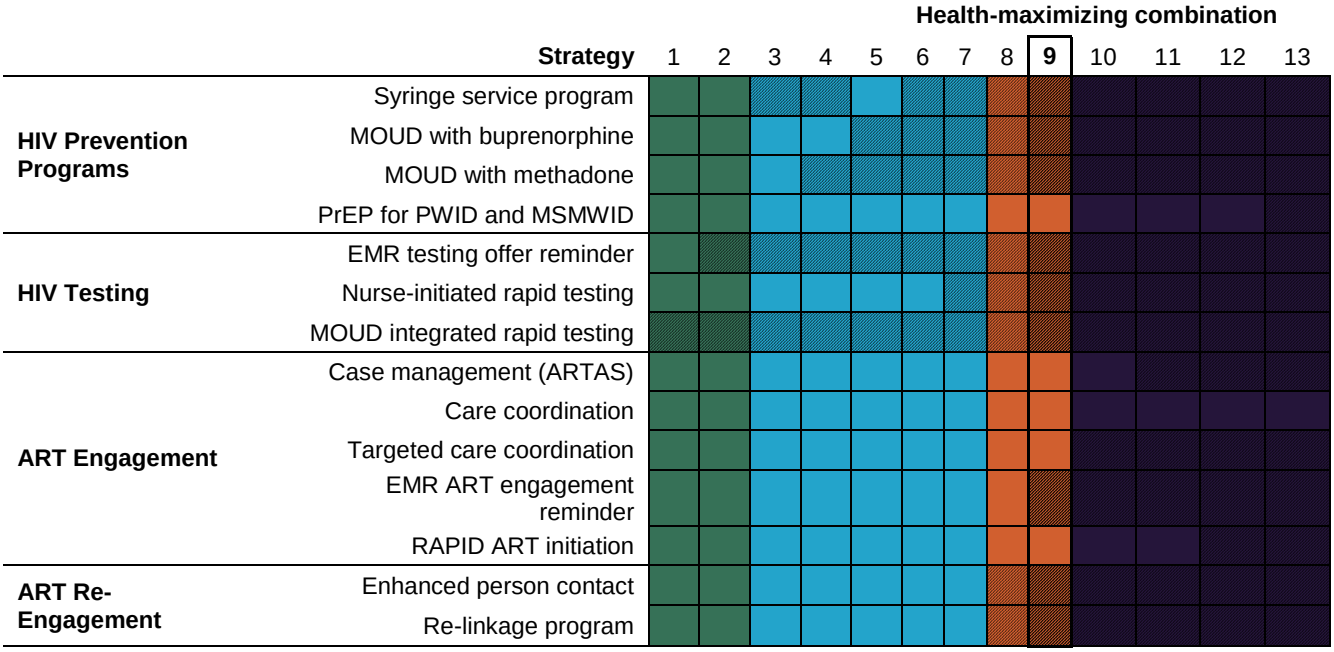
Los Angeles

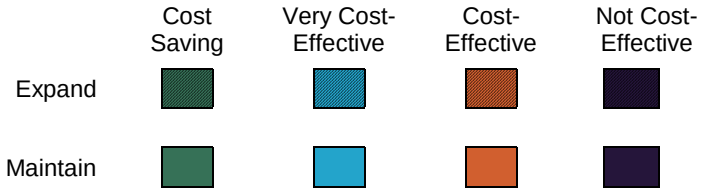
Strategy	*Incremental Cost: $M*	*Incremental QALYs*	*ICER: $ / QALY*
1	-3.8	201	CS
2	-2.6	811	CS
3	9.4	1,993	10,092
4	74.0	4,246	28,685
5	562.3	20,429	30,174
6	592.8	21,407	31,244
7	606.6	21,714	44,764
8	650.6	22,226	85,936
9	**714.0**	**22,900**	**94,069**
10	719.8	22,939	150,777
11	738.1	23,039	182,050
12	746.1	23,065	310,134
13	3435.3	25,214	1,251,625

$B: billions of $US; $M: millions of $US (both in 2018 $US); QALYs: quality-adjusted life years; ICER: incremental cost-effectiveness ratio; CS: cost-saving. Each of the strategies 1 through 8 represent the highest-valued strategies for a given investment level. Incremental costs and QALYs are compared against the next-most-costly strategy on the production function (i.e. Strategy 2 versus 1, 3 versus 2 etc.).

LOS ANGELES

Supplement Table 1. Panel B. Combination implementation strategies, delivered at optimistic implementation scale-up, residing on Los Angeles's health production function





QALY – Quality adjusted life year; ICER – Incremental cost-effectiveness ratio; MOUD – Medication for opioid use disorder; PrEP – Pre-exposure prophylaxis; MSM – men who have sex with men; EMR – Electronic medical record; ARTAS – Anti-Retroviral Treatment and Access to Services; ART – Antiretroviral therapy; RAPID – Rapid ART Program for Individuals with an HIV Diagnosis.

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LOS ANGELES

Supplement Table 1. Panel C. Incremental costs, QALYs and incremental cost-effectiveness ratios (ICER) of individual interventions

Intervention	Los Angeles		
HIV prevention programs	*ΔTC ($M)*	*ΔQALYs*	*ICER ($'000s)*
Syringe service program	8.0 [-97.3 - 137.7]	1270 [-165 - 2434]	6.3 [CS - 653.1]
MOUD with buprenorphine	499.0 [327.1 - 1284.0]	17057 [11199 - 22684]	29.3 [19.6 - 82.3]
MOUD with methadone	62.5 [1.4 - 179.2]	2258 [1127 - 3332]	27.7 [0.5 - 136.3]
PrEP for PWID and MSMWID	2605.2 [2165.4 - 3274.3]	3227 [1306 - 4256]	807.4 [574.7 - 2202.6]
HIV Testing			
EMR testing offer reminder	0.4 [-81.6 - 65.6]	658 [-296 - 1595]	0.7 [CS - 318.7]
Nurse-initiated rapid testing	4.1 [-85.4 - 67.9]	598 [-276 - 1705]	6.9 [CS - 395.0]
MOUD integrated rapid testing	-3.8 [-72.1 - 58.9]	201 [-659 - 1082]	CS [CS - 286.0]
ART engagement			
Case management (ARTAS)	17.1 [-47.8 - 88.6]	90 [-794 - 981]	190.8 [CS - 953.5]
Care coordination	30.1 [-33.0 - 104.8]	60 [-805 - 957]	500.5 [CS - 1991.8]
Targeted care coordination	6.2 [-61.3 - 71.4]	48 [-814 - 946]	130.2 [CS - 390.6]
EMR ART engagement reminder	66.0 [-22.7 - 142.6]	756 [-307 - 1604]	87.4 [CS - 959.0]
RAPID ART initiation	8.8 [-61.1 - 73.9]	31 [-821 - 923]	284.8 [CS - 465.6]
ART re-engagement			
Enhanced personal contact	28.1 [-40.3 - 96.4]	334 [-588 - 1202]	84.0 [CS - 1186.2]
Re-linkage program	17.2 [-48.9 - 84.4]	213 [-694 - 1099]	80.5 [CS - 893.3]

* Values represent the results obtained from the deterministic analysis and the 95% credible interval in brackets from the probabilistic sensitivity analysis over 2,000 simulations.
QALY: Quality-adjusted life years; TC: Total costs; CS: Cost-saving; PWID: People who inject drugs; MSM: Men who have sex with men; PrEP: Pre-exposure prophylaxis; MOUD: Medication for opioid use disorder; ART: Antiretroviral therapy; EMR: Electronic medical records; RAPID: Rapid ART Program for Individuals with an HIV Diagnosis.

MIAMI

Supplement Table 1. Panel A. Results of incremental cost-effectiveness analysis for combination implementation strategies comprising Miami's health production function

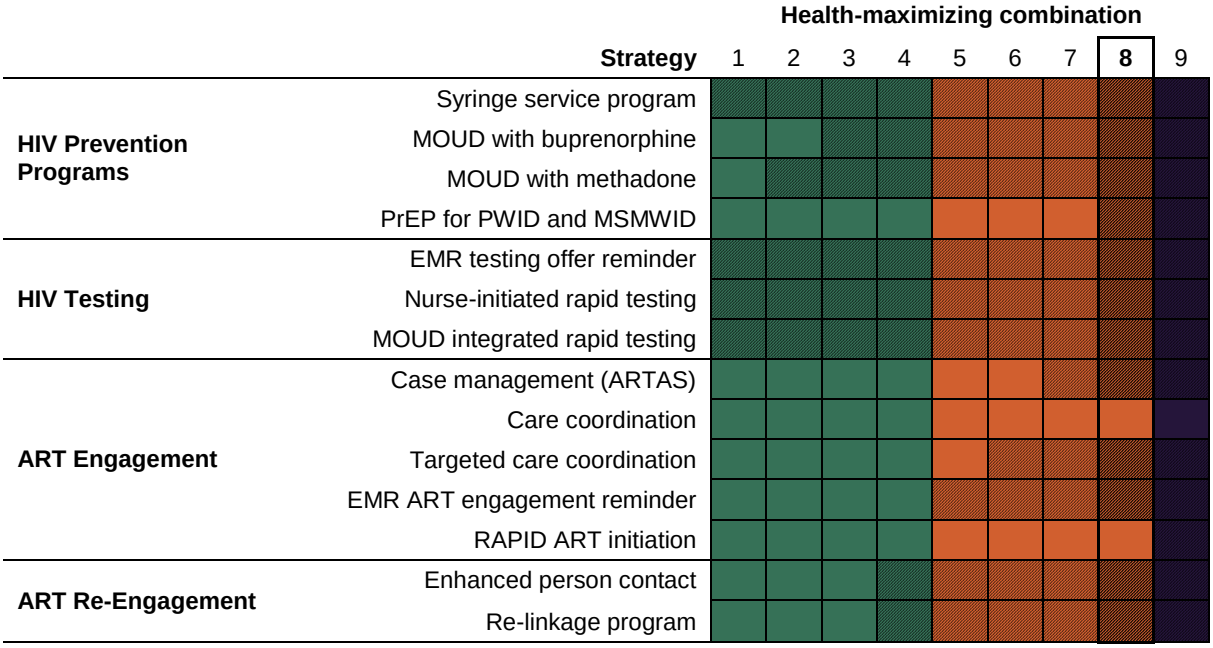
Miami

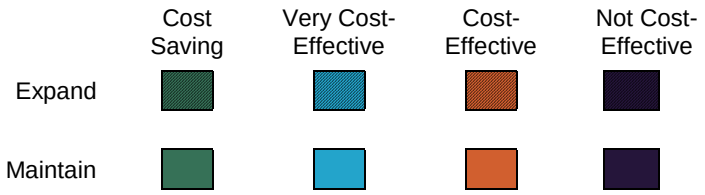
Strategy	*Incremental Cost: $M*	*Incremental QALYs*	*ICER: $ / QALY*
1	-237.2	5,273	CS
2	-235.1	5,367	CS
3	-48.1	13,314	CS
4	-17.2	13,773	CS
5	21.0	14,314	70,652
6	25.2	14,355	104,079
7	48.4	14,551	118,613
8	**643.3**	**18,618**	**146,256**
9	649.2	18,647	204,299

$B: billions of $US; $M: millions of $US (both in 2018 $US); QALYs: quality-adjusted life years; ICER: incremental cost-effectiveness ratio; CS: cost-saving. Each of the strategies 1 through 8 represent the highest-valued strategies for a given investment level. Incremental costs and QALYs are compared against the next-most-costly strategy on the production function (i.e. Strategy 2 versus 1, 3 versus 2 etc.).

MIAMI

Supplement Table 1. Panel B. Combination implementation strategies, delivered at optimistic implementation scale-up, residing on Miami's health production function





QALY – Quality adjusted life year; ICER – Incremental cost-effectiveness ratio; MOUD – Medication for opioid use disorder; PrEP – Pre-exposure prophylaxis; MSM – men who have sex with men; EMR – Electronic medical record; ARTAS – Anti-Retroviral Treatment and Access to Services; ART – Antiretroviral therapy; RAPID – Rapid ART Program for Individuals with an HIV Diagnosis.

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MIAMI

Supplement Table 1. Panel C. Incremental costs, QALYs and incremental cost-effectiveness ratios (ICER) of individual interventions

Intervention	Miami		
HIV prevention programs	*ΔTC ($M)*	*ΔQALYs*	*ICER ($'000s)*
Syringe service program	-214.9 [-701.8 - 100.8]	3507 [-199 - 11821]	CS [CS - 203.4]
MOUD with buprenorphine	148.7 [-113.9 - 512.8]	8378 [4904 - 14020]	17.7 [CS - 81.1]
MOUD with methadone	1.7 [-184.5 - 186.3]	102 [-1461 - 1746]	16.6 [CS - 248.3]
PrEP for PWID and MSMWID	415.5 [-476.3 - 961.9]	7007 [1385 - 21243]	59.3 [CS - 651.6]
HIV Testing			
EMR testing offer reminder	-23.0 [-239.7 - 163.8]	1244 [-657 - 4164]	CS [CS - 491.3]
Nurse-initiated rapid testing	-17.2 [-235.6 - 166.9]	1059 [-758 - 4361]	CS [CS - 485.8]
MOUD integrated rapid testing	-3.5 [-192.9 - 180.6]	141 [-1420 - 1771]	CS [CS - 134.6]
ART engagement			
Case management (ARTAS)	21.5 [-162.7 - 205.1]	192 [-1388 - 1851]	112.0 [CS - 796.4]
Care coordination	23.3 [-160.5 - 205.9]	59 [-1506 - 1692]	393.9 [CS - 520.6]
Targeted care coordination	4.7 [-182.2 - 186.4]	55 [-1493 - 1692]	85.7 [CS - 119.6]
EMR ART engagement reminder	41.2 [-145.9 - 215.9]	657 [-1087 - 2379]	62.7 [CS - 1046.5]
RAPID ART initiation	7.2 [-179.3 - 189.3]	49 [-1507 - 1684]	148.7 [CS - 164.2]
ART re-engagement			
Enhanced personal contact	20.2 [-170.6 - 201.0]	326 [-1253 - 1966]	62.1 [CS - 880.9]
Re-linkage program	12.7 [-173.6 - 193.9]	209 [-1380 - 1890]	60.8 [CS - 638.5]

* Values represent the results obtained from the deterministic analysis and the 95% credible interval in brackets from the probabilistic sensitivity analysis over 2,000 simulations.
QALY: Quality-adjusted life years; TC: Total costs; CS: Cost-saving; PWID: People who inject drugs; MSM: Men who have sex with men; PrEP: Pre-exposure prophylaxis; MOUD: Medication for opioid use disorder; ART: Antiretroviral therapy; EMR: Electronic medical records; RAPID: Rapid ART Program for Individuals with an HIV Diagnosis.

NEW YORK CITY

Supplement Table 1. Panel A. Results of incremental cost-effectiveness analysis for combination implementation strategies comprising New York City's health production function

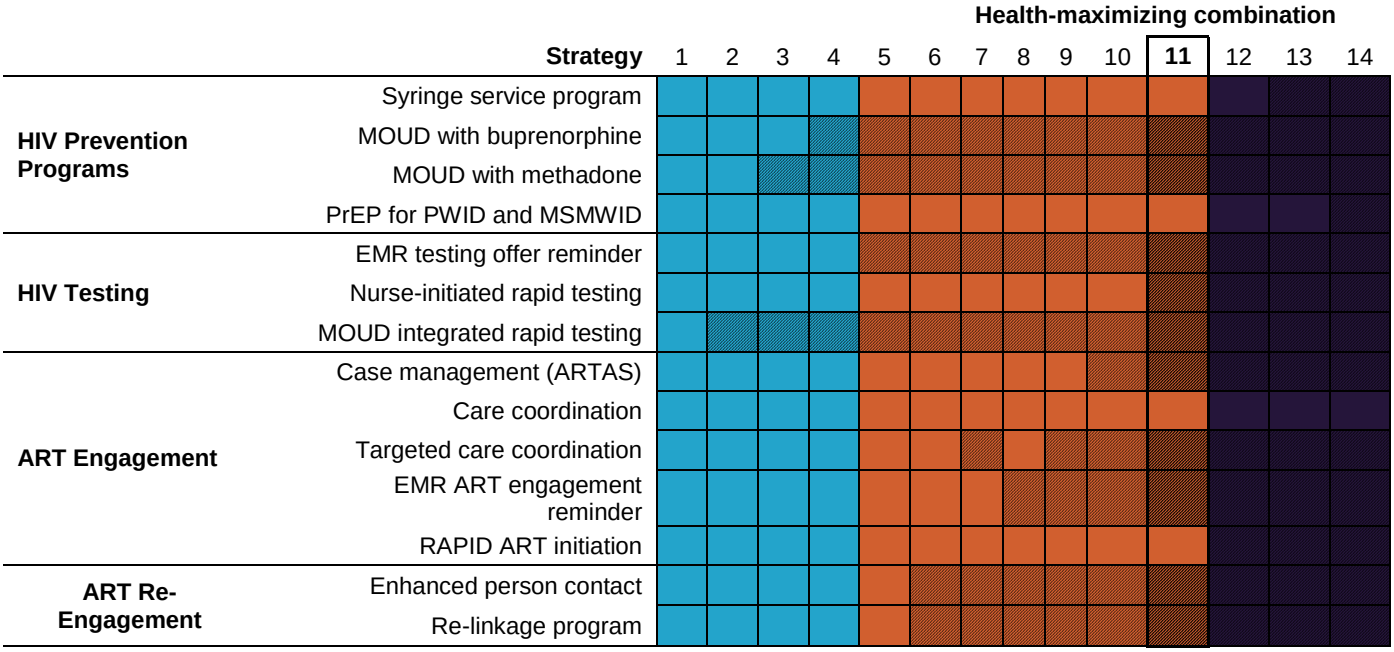
New York City

Strategy	*Incremental Cost: $M*	*Incremental QALYs*	*ICER: $ / QALY*
1	0.0	0	0
2	0.1	90	1,008
3	61.2	1,884	34,100
4	765.4	21,772	35,407
5	788.7	22,104	70,161
6	896.0	23,357	85,581
7	907.6	23,487	89,716
8	1066.9	25,201	92,922
9	1077.2	25,310	95,126
10	1089.9	25,412	123,105
11	**1115.8**	**25,615**	**128,387**
12	1120.0	25,634	220,893
13	1263.9	25,997	395,568
14	4975.3	26,666	5,553,489

$B: billions of $US; $M: millions of $US (both in 2018 $US); QALYs: quality-adjusted life years; ICER: incremental cost-effectiveness ratio; CS: cost-saving. Each of the strategies 1 through 8 represent the highest-valued strategies for a given investment level. Incremental costs and QALYs are compared against the next-most-costly strategy on the production function (i.e. Strategy 2 versus 1, 3 versus 2 etc.).

NEW YORK CITY

Supplement Table 1. Panel B. Combination implementation strategies, delivered at optimistic implementation scale-up, residing on New York City's health production function



QALY – Quality adjusted life year; ICER – Incremental cost-effectiveness ratio; MOUD – Medication for opioid use disorder; PrEP – Pre-exposure prophylaxis; MSM – men who have sex with men; EMR – Electronic medical record; ARTAS – Anti-Retroviral Treatment and Access to Services; ART – Antiretroviral therapy; RAPID – Rapid ART Program for Individuals with an HIV Diagnosis.

† The health-maximizing strategy that remained cost-effective was determined by calculating the incremental cost-effectiveness ratio, defined as the additional cost of a specific combination implementation strategy divided by its additional health benefit, as compared with the next-most-costly strategy on the health production function. Combination implementation strategies with ICERs less than $50,000/QALY were considered very cost-effective, while those with ICERs < $150,000/QALY were considered cost-effective. The numerator represents the total increment in healthcare costs (in 2018 US$) for the adult population (aged 15-64) in a given city, and the denominator represents the total gain in quality-adjusted life years for this group.

NEW YORK CITY

Supplement Table 1. Panel C. Incremental costs, QALYs and incremental cost-effectiveness ratios (ICER) of individual interventions

Intervention	New York City		
HIV prevention programs	*ΔTC ($M)*	*ΔQALYs*	*ICER ($'000s)*
Syringe service program	142.9 [38.0 - 230.8]	497 [-441 - 2149]	287.4 [CS - 3262.1]
MOUD with buprenorphine	703.0 [391.2 - 1754.8]	19667 [12557 - 28621]	35.7 [22.1 - 86.8]
MOUD with methadone	61.3 [-1.3 - 205.0]	1781 [994 - 3463]	34.4 [CS - 153.9]
PrEP for PWID and MSMWID	3707.1 [3072.1 - 4449.9]	1045 [65 - 3155]	3548.4 [738.8 - 9019.2]
HIV Testing			
EMR testing offer reminder	21.8 [-56.6 - 99.5]	415 [-395 - 1459]	52.5 [CS - 1062.1]
Nurse-initiated rapid testing	22.1 [-56.4 - 96.8]	344 [-441 - 1440]	64.4 [CS - 1092.9]
MOUD integrated rapid testing	0.1 [-71.4 - 78.5]	90 [-756 - 880]	1.0 [CS - 407.1]
ART engagement			
Case management (ARTAS)	12.0 [-53.9 - 96.8]	93 [-748 - 872]	129.1 [CS - 892.1]
Care coordination	52.0 [-14.5 - 150.7]	115 [-734 - 865]	452.8 [CS - 2228.2]
Targeted care coordination	12.4 [-58.1 - 91.8]	146 [-677 - 908]	85.1 [CS - 885.9]
EMR ART engagement reminder	192.6 [46.2 - 317.0]	2154 [443 - 3637]	89.4 [27.4 - 290.2]
RAPID ART initiation	4.4 [-65.9 - 82.5]	22 [-821 - 783]	197.8 [CS - 465.2]
ART re-engagement			
Enhanced personal contact	71.7 [-11.9 - 167.7]	845 [-95 - 1782]	84.9 [CS - 773.6]
Re-linkage program	45.1 [-28.9 - 132.2]	541 [-380 - 1506]	83.5 [CS - 1192.6]

* Values represent the results obtained from the deterministic analysis and the 95% credible interval in brackets from the probabilistic sensitivity analysis over 2,000 simulations.
QALY: Quality-adjusted life years; TC: Total costs; CS: Cost-saving; PWID: People who inject drugs; MSM: Men who have sex with men; PrEP: Pre-exposure prophylaxis; MOUD: Medication for opioid use disorder; ART: Antiretroviral therapy; EMR: Electronic medical records; RAPID: Rapid ART Program for Individuals with an HIV Diagnosis.

SEATTLE

Supplement Table 1. Panel A. Results of incremental cost-effectiveness analysis for combination implementation strategies comprising Seattle's health production function

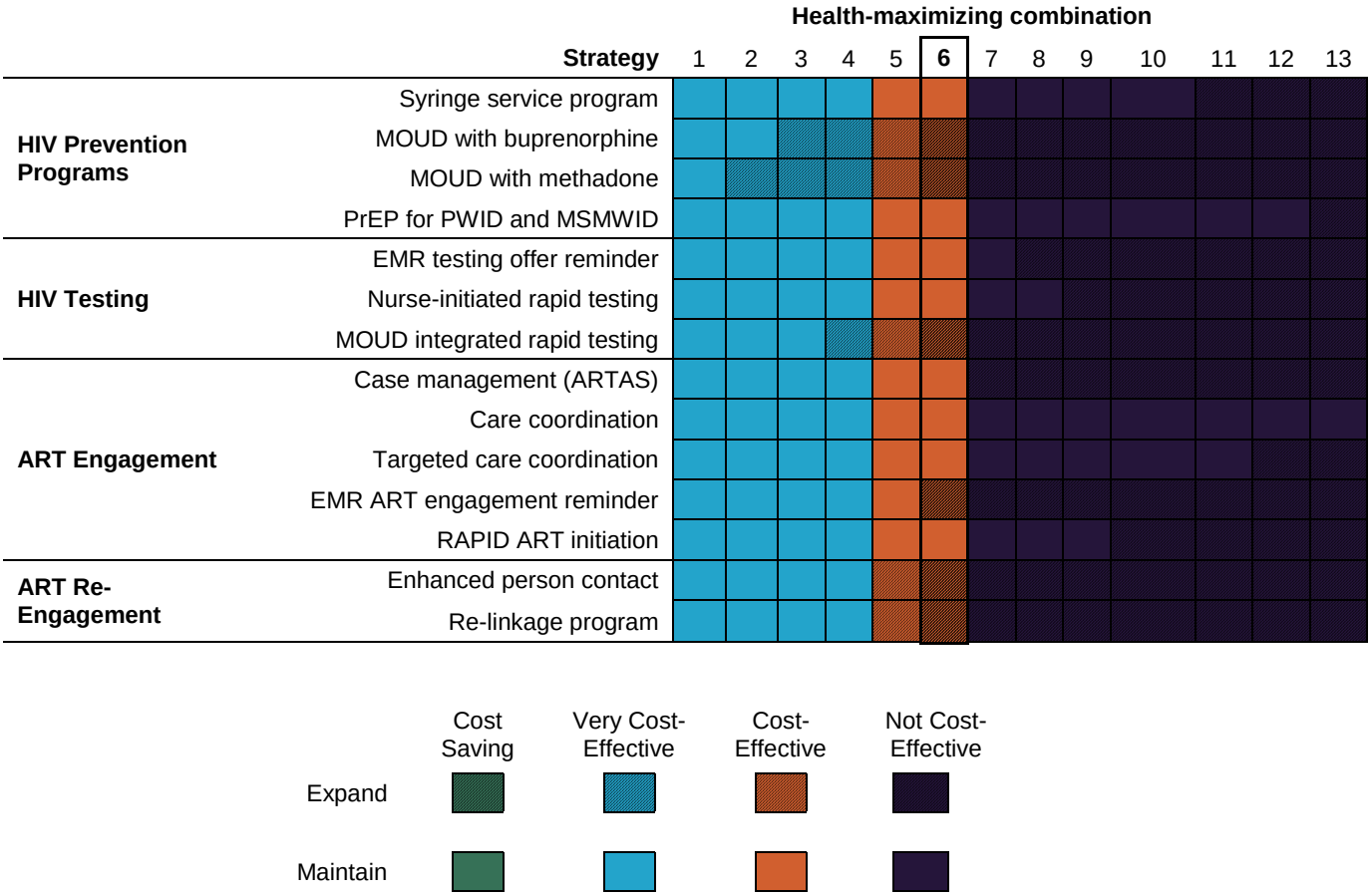
Seattle

Strategy	*Incremental Cost: $M*	*Incremental QALYs*	*ICER: $ / QALY*
1	0.0	0	0
2	12.9	455	28,386
3	175.0	5,852	30,029
4	175.8	5,874	34,270
5	177.1	5,890	87,293
6	**180.1**	**5,914**	**127,920**
7	181.6	5,923	156,381
8	187.2	5,953	185,421
9	192.7	5,971	300,871
10	193.4	5,973	353,847
11	225.4	6,035	519,615
12	225.8	6,035	821,837
13	1232.4	6,123	11,433,491

$B: billions of $US; $M: millions of $US (both in 2018 $US); QALYs: quality-adjusted life years; ICER: incremental cost-effectiveness ratio; CS: cost-saving. Each of the strategies 1 through 8 represent the highest-valued strategies for a given investment level. Incremental costs and QALYs are compared against the next-most-costly strategy on the production function (i.e. Strategy 2 versus 1, 3 versus 2 etc.).

SEATTLE

Supplement Table 1. Panel B. Combination implementation strategies, delivered at optimistic implementation scale-up, residing on Seattle's health production function



QALY – Quality adjusted life year; ICER – Incremental cost-effectiveness ratio; MOUD – Medication for opioid use disorder; PrEP – Pre-exposure prophylaxis; MSM – men who have sex with men; EMR – Electronic medical record; ARTAS – Anti-Retroviral Treatment and Access to Services; ART – Antiretroviral therapy; RAPID – Rapid ART Program for Individuals with an HIV Diagnosis.

† The health-maximizing strategy that remained cost-effective was determined by calculating the incremental cost-effectiveness ratio, defined as the additional cost of a specific combination implementation strategy divided by its additional health benefit, as compared with the next-most-costly strategy on the health production function. Combination implementation strategies with ICERs less than $50,000/QALY were considered very cost-effective, while those with ICERs < $150,000/QALY were considered cost-effective. The numerator represents the total increment in healthcare costs (in 2018 US$) for the adult population (aged 15-64) in a given city, and the denominator represents the total gain in quality-adjusted life years for this group.

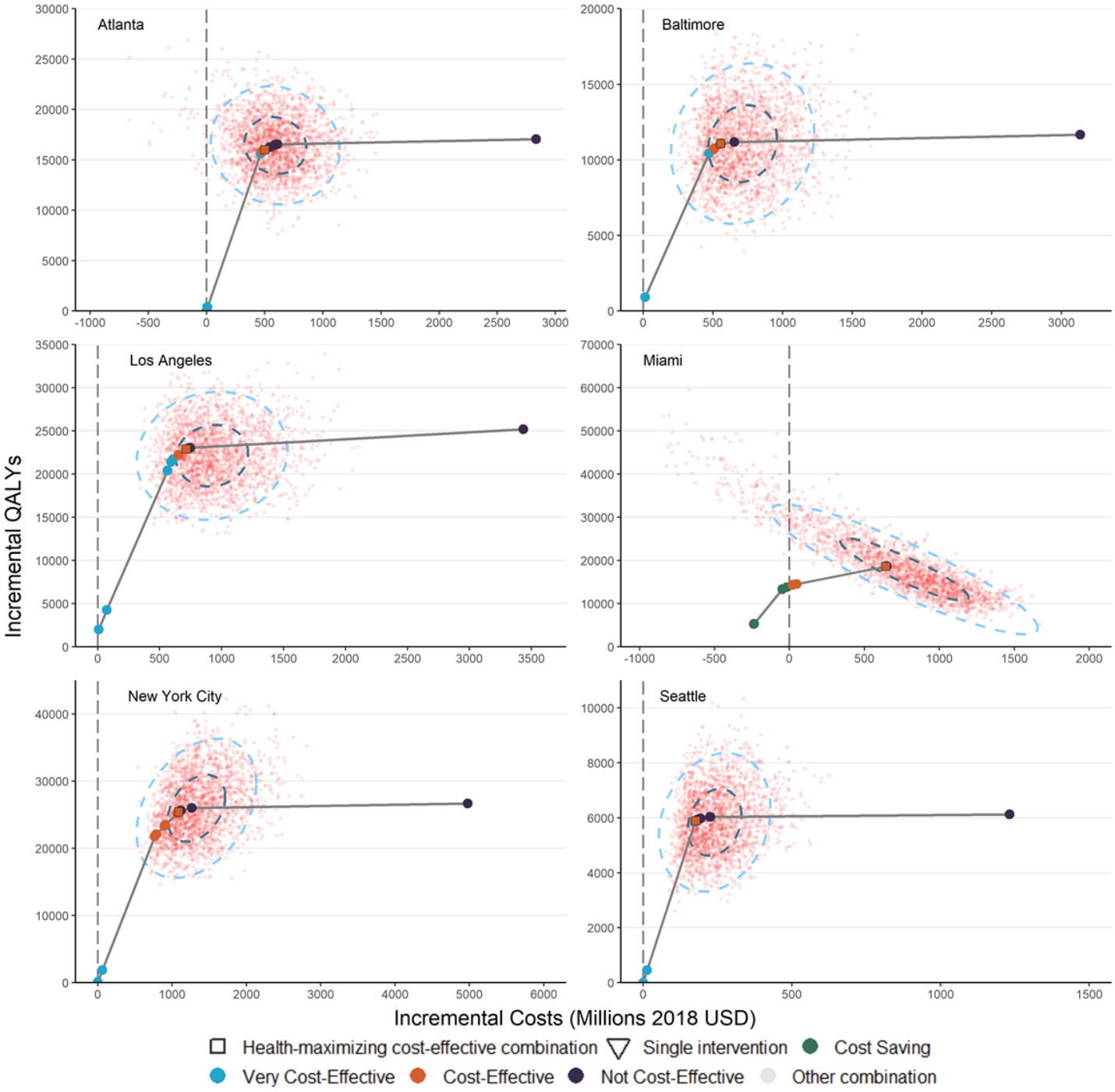
SEATTLE

Supplement Table 1. Panel C. Incremental costs, QALYs and incremental cost-effectiveness ratios (ICER) of individual interventions

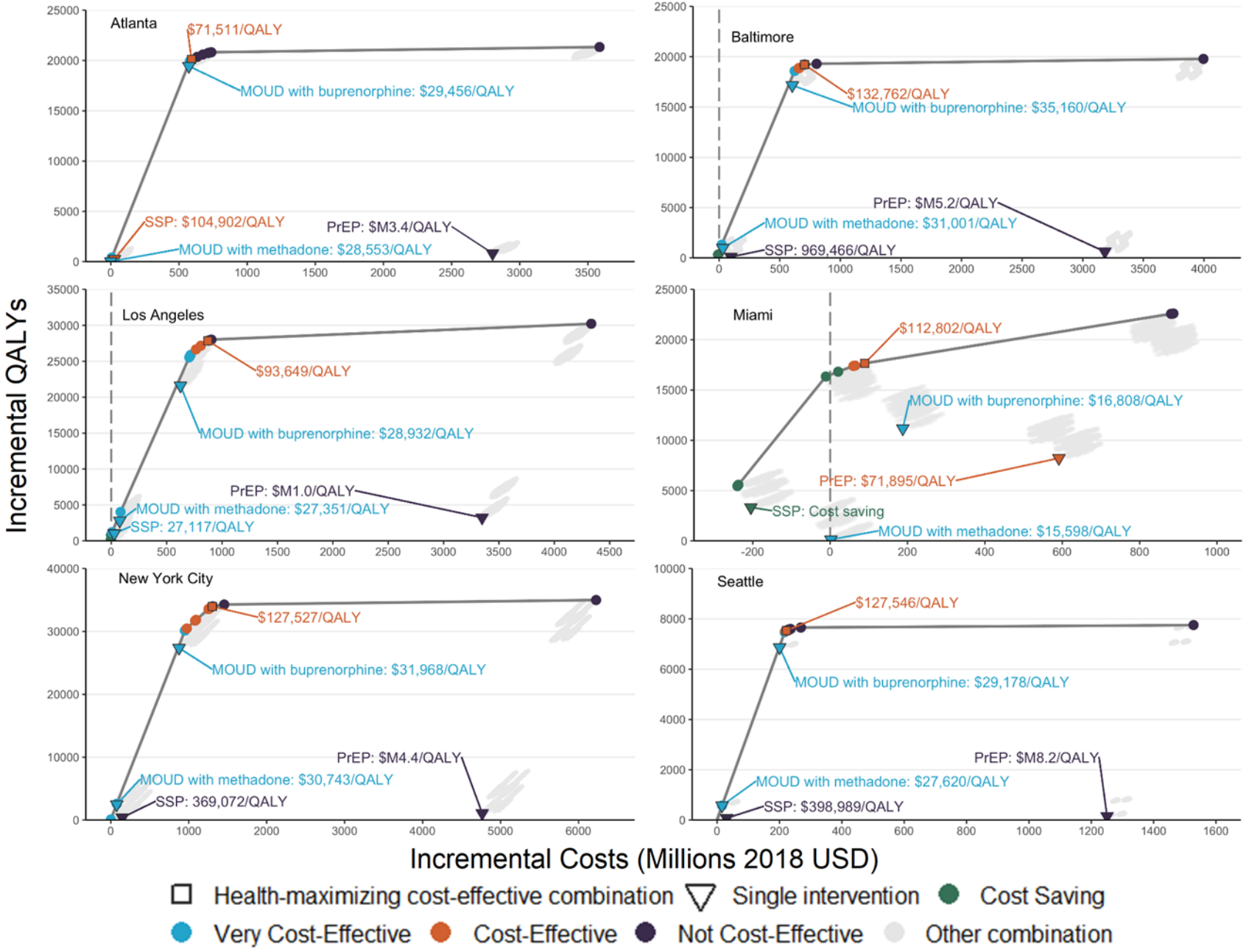
Intervention	Seattle		
HIV prevention programs	*ΔTC ($M)*	*ΔQALYs*	*ICER ($'000s)*
Syringe service program	29.8 [19.1 - 58.2]	83 [-5 - 109]	359.6 [CS - 7469.5]
MOUD with buprenorphine	161.5 [102.4 - 423.4]	5375 [3368 - 7649]	30.1 [19.7 - 81.7]
MOUD with methadone	12.9 [4.6 - 32.7]	455 [311 - 585]	28.4 [10.2 - 80.6]
PrEP for PWID and MSMWID	998.8 [836.1 - 1207.8]	140 [65 - 160]	7159.7 [5598.2 - 9907.4]
HIV Testing			
EMR testing offer reminder	5.5 [-3.3 - 13.4]	39 [15 - 57]	141.0 [CS - 601.5]
Nurse-initiated rapid testing	5.4 [-3.4 - 13.5]	35 [10 - 64]	156.5 [CS - 815.7]
MOUD integrated rapid testing	0.3 [-7.1 - 8.4]	9 [-7 - 24]	37.3 [CS - 2264.4]
ART engagement			
Case management (ARTAS)	1.4 [-5.8 - 9.6]	9 [-7 - 24]	157.5 [CS - 2944.2]
Care coordination	6.7 [-0.3 - 17.8]	3 [-11 - 17]	2617.5 [CS - 7919.4]
Targeted care coordination	0.4 [-6.7 - 8.7]	1 [-13 - 15]	510.5 [CS - 5520.6]
EMR ART engagement reminder	3.4 [-4.8 - 11.1]	28 [4 - 49]	120.8 [CS - 760.7]
RAPID ART initiation	0.7 [-6.6 - 8.8]	2 [-12 - 16]	317.3 [CS - 4225.1]
ART re-engagement			
Enhanced personal contact	1.0 [-6.3 - 9.0]	11 [-5 - 27]	89.6 [CS - 1529.7]
Re-linkage program	0.7 [-6.6 - 8.7]	7 [-8 - 22]	104.6 [CS - 2305.9]

* Values represent the results obtained from the deterministic analysis and the 95% credible interval in brackets from the probabilistic sensitivity analysis over 2,000 simulations.
QALY: Quality-adjusted life years; TC: Total costs; CS: Cost-saving; PWID: People who inject drugs; MSM: Men who have sex with men; PrEP: Pre-exposure prophylaxis; MOUD: Medication for opioid use disorder; ART: Antiretroviral therapy; EMR: Electronic medical records; RAPID: Rapid ART Program for Individuals with an HIV Diagnosis.

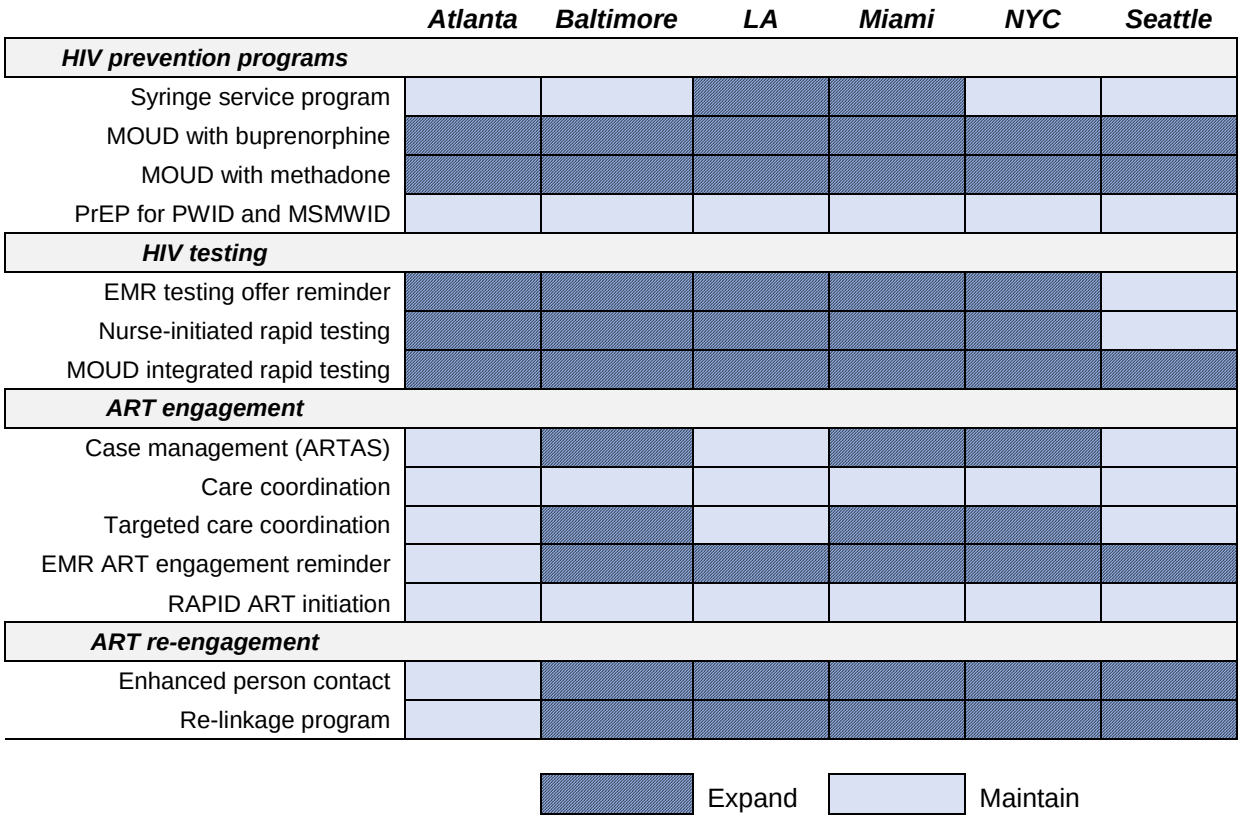
Supplemental Figure 1. Probabilistic sensitivity analysis displaying uncertainty surrounding optimal combination implementation strategies (with 50% and 95% uncertainty ellipses)



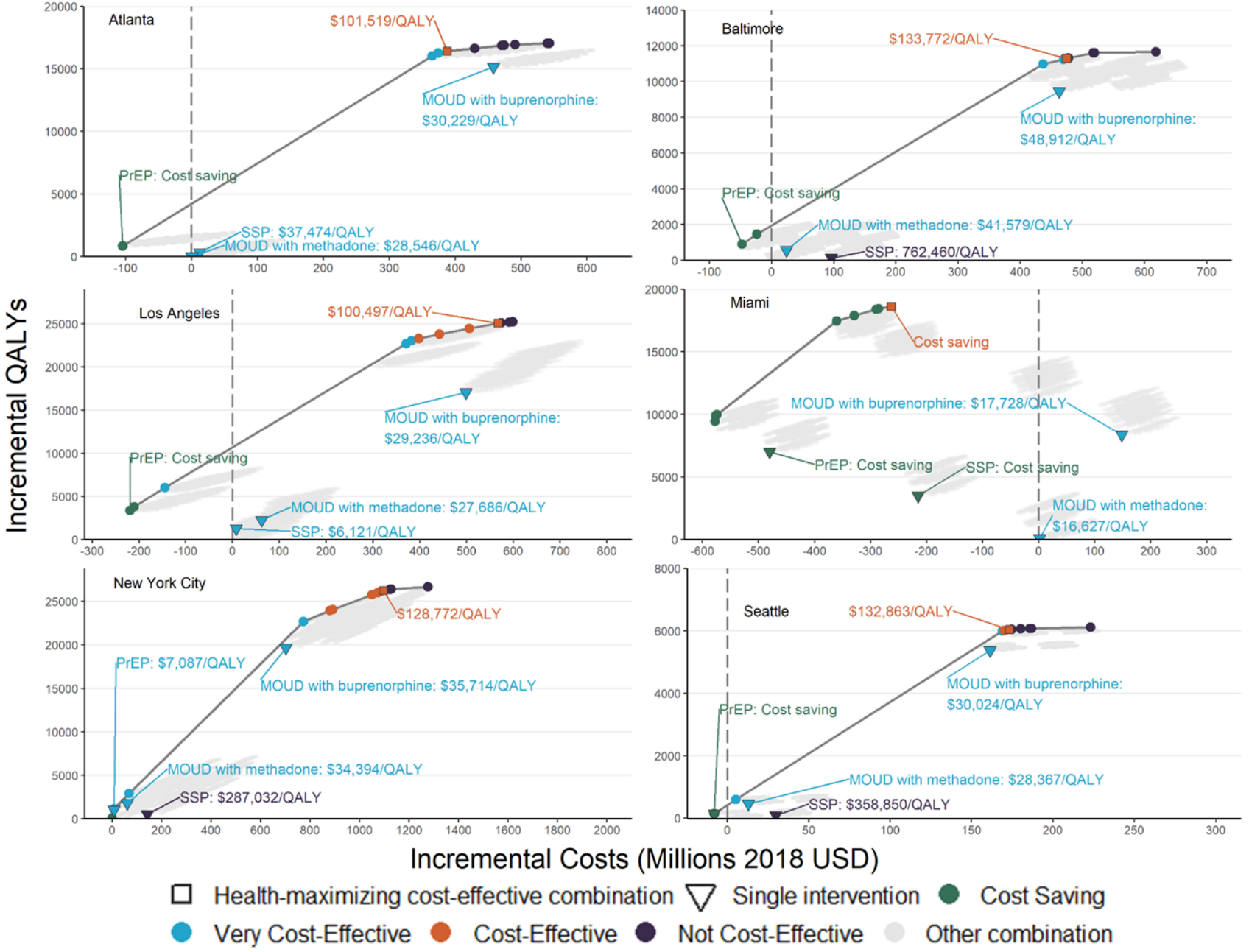
Supplement Figure 2. City-level health production functions for the changing opioid epidemic scenario



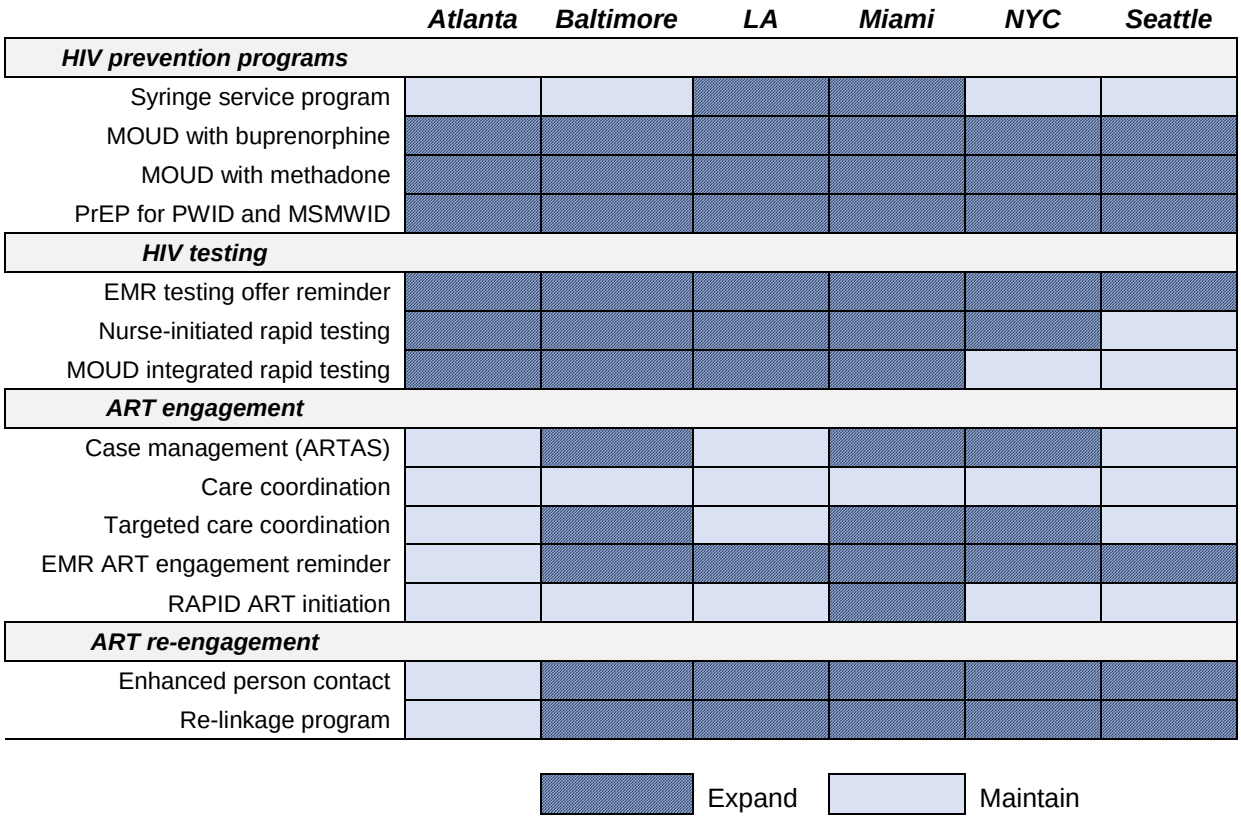
Supplement Figure 3. Interventions included in the health-maximizing cost-effective combinations for the changing opioid epidemic scenario



Supplement Figure 4. City-level health production functions for the Free PrEP scenario



Supplement Figure 5. Interventions included in the health-maximizing cost-effective combinations for the free PrEP scenario



Supplement Figure 6. Interventions excluded from combinations

		HIV Prevention Programs				*HIV Testing*			*ART Engagement*					*ART Re-Engagement*	
		P1	P2	P3	P4	D3	D4	D5	T1	T2	T3	T4	T5	T6	T7
HIV Prevention Programs	Syringe service program														
	MOUD with buprenorphine														
	MOUD with methadone														
	PrEP for PWID and MSMWID														
HIV Testing	EMR testing offer reminder (EMR)														
	Nurse-initiated rapid testing (Nurse)														
	MOUD integrated rapid testing (MOUD testing)														
ART Engagement	Case management (ARTAS)														
	Care coordination														
	Targeted care coordination														
	EMR ART engagement reminder														
	RAPID ART initiation														
ART Re-Engagement	Enhanced person contact														
	Re-linkage program														

Shaded areas indicate excluded combinations that would not practically be implemented jointly, such as care coordination delivered to the full population of PLHIV and the same care coordination intervention targeted to individuals with CD4 <200 cells/μL.

Supplemental Table 2. Costs attributable to the implementation and delivery of HIV prevention programs (2018 USD)

Intervention	Implementation Cost*		Delivery Cost	
	$ (95% CI)	Description	$ (95% CI)	Description
Syringe service program (SSP)				
One-time costs for scale-up	16,111 (11,194-21,133)	Start-up costs	1.24 (0.92-1.56)	Cost per syringe, including overhead
Medication for opioid use disorder (MOUD)				
Buprenorphine	1,276.92†	Costs per prescribing physician	414.81 (274.67-1,141.81)	Monthly costs per person"
Methadone	4,481.54†	Costs per OTP	184.28 (146.61-229.19)	Monthly costs per person"
Pre-exposure prophylaxis (PrEP)				
	177.00†	Costs per prescribing physician	883.83 (631.94-1,177.27)	Monthly costs per person
			34.37 (11.46-68.75)	Costs for consultation per individual**

MSM: Men who have sex with men; MWID: MSM who inject drugs; CI: Confidence interval.

* Costs in the model are applied monthly per individual, all assumptions and calculations have been presented elsewhere

" Costs include costs attributable to toxicology and overhead.

** Costs include costs attributable to HIV screening.

† 95% CI for monthly costs applied in the model were derived based on the ranges of setting-specific patient volumes.

Supplemental Table 2. CHEERS checklist

Section/Item	Item	Recommendation	Reported on page no.
Title and Abstract			
Title	1	Identify the study as an economic evaluation	Title page
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods, results, and conclusions	Abstract
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study	Introduction – Page 3
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen	Krebs et al. (2019)[6] – Page 4 (Paragraph 3)
Setting and location	5	State relevant aspects of the system in which decisions need to be made	Methods – Page 5 (Paragraph 1)
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated	Methods – Page 8 (Paragraph 2)
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen	Methods – Page 7/8 (Paragraph 2-4)
Time horizon	8	State the time horizons over which costs and consequences are being evaluated	Methods – Page 8 (Paragraph 2)
Discount rate	9	Report/explain the choice of discount rate used for costs and outcomes	Methods – Page 8 (Paragraph 2)
Choice of health outcomes	10	Describe what outcomes were used as the measure of benefit in the evaluation and their relevance for the analysis	Methods – Page 8 (Paragraph 2)
Measurement of effectiveness	11	Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data	Krebs et al. (2019)[6] – S1 Supplement Table B2 & Pg. 23-32
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes	Krebs et al. (2019)[6] – S1 Supplement Page 49 (Section 6)
Estimating resources and costs	13	Describe approaches and data sources used to estimate resource use associated with model health states	Krebs et al. (2019)[6] – Page 11 (Paragraph 9), Krebs et al. (2019)[7]
Currency, price date and conversion	14	Report the dates of the estimated resource quantities and unit costs	Methods – Page 8 (Paragraph 2)
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used	Zang et al. (2019)[9] – Methods (2.1.1 Model construction)

Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model	Zang et al. (2019)[9] – Methods (2.1 Model description)
Analytical methods	17	Describe all analytical methods supporting the evaluation	Krebs et al. (2019)[6] – S1 Supplement C
Results			
Study parameters	18	Report the values, ranges, references, and probability distributions for all parameters	Krebs et al. (2019)[6] – S1 Supplement C & S2 Supplement "Supplement C Tables"
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between comparator groups	Krebs et al. (2019)[7]
Characterising uncertainty	20	Describe the effects on the results of uncertainty for all input parameters and uncertainty related to the structure of the model and assumptions	Supplement Tables 1 & Figures 1-5
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients	Discussion – Heterogeneity discussed throughout
Discussion			
Findings, limitations, generalisability, and current knowledge	22	Summarize key findings and describe how they support the conclusions reached, and limitations to generalisability	Discussion – Page 12 (Paragraph 1) & Page 15 (Paragraph 3)
Other			
Source of funding	23	Describe study funding and other non-monetary sources of support	Acknowledgements
Conflicts of interest	24	Describe any potential conflicts of interest	Declarations of interests

Impact inventory

Sector	Type of Impact	Perspective		Notes
		Third-Party Payer	Societal	
Formal Health Care				
Health	**Health Outcomes (Effects)**			
	Longevity	√		Longevity effects captured through QALYs until individuals age-out at 65 years
	HRQoL	√		Longevity and HRQoL captured in QALYs
	Other Health Effects	√		Incident HIV infections
	Medical Costs			
	Third-Party Payers	√		Percentage of health resource use costs + all intervention-related costs (i.e. all incremental costs above the status quo)
	Patients out-of-pocket	√		Percentage of health resource use costs in status quo
	Future related medical costs	√		Captured in health resource use costs for status quo and intervention scenarios
	Future unrelated medical costs	√		Captured in background health resource use costs among HIV-negative individuals
Informal Health Care				
Health	**Patient-time costs**	N/A		
	Unpaid caregiver-time costs	N/A		
	Transportation costs	N/A		
Non-Health Care Sectors				
Productivity	**Labour market earnings lost**	N/A		
	Cost of unpaid lost productivity	N/A		
	Cost of uncompensated household production	N/A		
Consumption	**Future consumption unrelated to health**	N/A		
Social Services	**Cost of social services related to intervention**	N/A		
Legal or criminal justice	**Number of crimes related to intervention**	N/A		
	Cost of crimes related to intervention	N/A		
Education	**Impact on educational achievement**	N/A		
Housing	**Cost of intervention on home improvements**	N/A		
Environment	**Production of toxic waste by intervention**	N/A		
Other	**Other impacts**	N/A		

HRQoL – Health-related quality of life; QALY – Quality adjusted life-year

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