Title

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

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Abstract - [194/200 words]

Background: Persons who inject drugs (PWID) are at a disproportionately high risk of HIV infection. We aimed to determine the highest-valued combination implementation strategies to reduce the burden of HIV among PWID in six US cities.

Methods: Using a dynamic HIV transmission model calibrated for Atlanta, Baltimore, Los Angeles, Miami, New York City and Seattle, we assessed the value of implementing combinations of evidence-based interventions at optimistic (drawn from best available evidence) or ideal (90% coverage) scale-up. We estimated reduction in HIV incidence among PWID, quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratios (ICERs) for each city (10-year implementation; 20-year horizon; 2018$US).

Results: Combinations that maximized health benefits contained between six (Atlanta and Seattle) and twelve (Miami) interventions with ICER values ranging from $94,069/QALY in Los Angeles to $146,256/QALY in Miami. These strategies would reduce HIV incidence among PWID in 2030 by 8.1% (2.8%, 13.2%) in Seattle to 54.4% (37.6%, 73.9%) in Miami. Incidence reduction reached 16.1% to 75.5% at ideal scale.

Conclusions: Evidence-based interventions targeted to PWID can deliver considerable value, however ending the HIV epidemic among PWID will require innovative implementation strategies and supporting programs to reduce social and structural barriers to care.

Key words

HIV; localized HIV microepidemics; interventions; cost-effectiveness; injection drug use; dynamic HIV transmission model

INTRODUCTION

In the United States, persons who inject drugs (PWID) continue to be disproportionately at risk of HIV infection. International and city-level successes have provided evidence that important reductions in HIV incidence among PWID are possible with the widespread provision of HIV care and services to prevent and reduce harms caused by substance use [1]. Domestically, the steady declines in HIV incidence among PWID has been a success story and several jurisdictions are now focused on preventing resurgence and getting new HIV infections attributed to drug injection to zero. Nonetheless, following the rise in prevalence of opioid injection, 2015 marked the first time in two decades that parenteral infections increased in the United States [2].

There is considerable evidence suggesting that broad implementation of prevention programs can be highly effective in reducing transmission of HIV and other blood-borne pathogens among PWID [1, 3, 4]. Nevertheless, the high prevalence of drug injection-related HIV infections among people living with HIV (18.1% in 2016) [5] and the lifetime prevalence of injection drug use in the United States (estimated to be 2.6%) [6] underscore how the public health response and short supply of these services have been (and remain) inadequate in many settings [1, 7, 8].

The US Centers for Disease Control and Prevention (CDC) have recommended a comprehensive approach to reduce the risk of HIV acquisition and transmission among PWID [9]. Long-standing recommendations include sterile syringe and needle distribution, and medication for opioid use disorders, both with robust evidence of effectiveness and cost-effectiveness [10-13]. In addition, the CDC's guidance includes expanded HIV testing and the provision of ART for treatment and prevention, the latter of which can have large independent effects on incidence reduction among PWID [4]. Although pre-exposure prophylaxis (PrEP) at current prices has not been found to be cost-effective among PWID in prior US-based modelling studies [12, 14], the US Preventive Services Task Force recently recommended that PrEP be offered to all persons at high risk of HIV acquisition, including PWID [15].

Prior evidence from modeling studies indicates that HIV incidence among PWID can be reduced substantially in well-resourced cities with high coverage of evidence-based interventions [16] and that focused, locally-oriented strategies in treating and preventing HIV provide the most value [17]. Simulation models can provide a unified framework to quantify the potential public health and economic impact of different strategies over the long-term, accounting for synergistic effects of multiple interventions and local context. Despite a consensus that combination implementation strategies are necessary to reduce HIV incidence among PWID [1, 3], determining which combination should be expanded across cities with different injection drug use epidemiology is necessary to deliver maximum value and produce the greatest impact.

Using a dynamic compartmental HIV transmission model populated and calibrated to replicate the epidemiological and structural conditions for six US cities, we aimed to determine the highest-valued combination implementation strategies to reduce the burden of HIV among PWID.

METHODS

Model description

Our analysis builds on a previously published dynamic, compartmental HIV transmission model adapted and calibrated to replicate city-level HIV microepidemics in Atlanta, Baltimore, Los Angeles, Miami, New York City, and Seattle. We selected these six cities because they represent nearly one-quarter of the population of persons living with HIV in the United States and the fact that they represent diverse HIV microepidemics with extensive epidemiological and structural differences in their public health responses to HIV [18]. This computer simulation model was based on a synthesis of the best available evidence on epidemiological and structural conditions for each city and has previously been described in detail elsewhere [7, 19]. The model tracked HIV-susceptible individuals through infection, diagnosis, treatment with ART and ART discontinuation. In each city, the adult population aged 15-64 was partitioned by sex at birth, HIV risk group (men who have sex with men [MSM], PWID, MSM who inject drugs [MSMWID] and heterosexuals), race/ethnicity (black/African American, Hispanic/Latinx and non-Hispanic white/others) and sexual risk behavior level (high- vs. low-risk).

We derived estimates of the size of the PWID population by multiplying race/ethnicity-stratified total population numbers by gender-weighted, race/ethnicity-specific prevalence estimates for each city. We assumed that gender proportions of PWID were equivalent within race/ethnicity strata and used prevalence estimates from the most recent available year [7, 20]. Given the uncertainty in population sizes for MSMWID, we derived population estimates by taking the average of two estimated population sizes: (i) the proportion of MSM that inject drugs and (ii) the proportion of male PWID that have sex with men [7, 19, 21-23]. Finally, based on the best available evidence, we assumed that 72.7% of PWID and MSMWID had an opioid use disorder [24].

HIV transmission within the model was possible between any two HIV-discordant individuals. The probability of HIV transmission was determined by: (i) the probability of selecting a partner living with HIV; (ii) the type of risk behavior engaged in (heterosexual or homosexual activity, or sharing injection equipment); (iii) the infected individual's HIV disease stage (acute or by CD4-based strata); (iv) the infected individual's ART status; (v) whether the uninfected individual was on PrEP; and (vi) the probability of condom use. We allowed for a combination of assortative and proportional sexual partnership mixing; assortative mixing accounted for individuals being more likely to form partnerships within a common stratum (e.g. race/ethnicity, risk behavior level), while proportional mixing accounted for individuals with many partners being more likely to select a partner who also had many partners. We also assumed proportional mixing among PWID (i.e., individuals who share many injections were more likely to select a partner who also shares many injections). Further details on the probability of HIV transmission in the model have previously been provided elsewhere [19].

The model also captured heterogeneity in maturation (e.g., rates at which individuals age out of the model) and mortality, and the disparities in accessing health, prevention and treatment services, including HIV testing, ART, syringe service programs (SSP), medication for opioid use disorder (MOUD), and PrEP.

Model calibration and validation

For each city, we calibrated the model to match HIV prevalence, new diagnoses and deaths (2012-2015), stratified by sex, race/ethnicity, and HIV risk group (17 targets total, including prevalence among PWID and MSMWID), and validated against external incidence estimates [19]. The model was used to project microepidemic trajectories over a 20-year time horizon (2020-2040), accounting for external estimates of population growth, which incorporated demographic shifts in race/ethnic composition for each city, to serve as the basis of comparison [25]. In the

projections, status quo service levels of prevention, testing and treatment services were held at their 2015 levels (Table 1) except for PrEP, which was held at 2017 levels to account for its recent rapid growth in uptake among MSM.

Interventions

We selected 14 evidence-based interventions within four specific domains (Table 2): HIV prevention programs (SSP, MOUD with either methadone or buprenorphine and PrEP); HIV testing; ART engagement (ART initiation and retention); and ART re-engagement (re-initiation and re-linkage). These interventions were selected from the US Centers for Disease Control and Prevention 'Compendium of Evidence-Based Interventions and Best Practices for HIV Prevention' and from the recently published literature [27, 28].

Although the model captured outcomes across risk groups for the entire adult population in each city, the implementation of interventions in our analysis was targeted exclusively to PWID and MSMWID (jointly referred to as PWID hereafter). Access to health services were held at status quo levels among the non-PWID population in each of the scenarios we describe below. Scale-up from status quo service levels was implemented proportionally across risk and ethnic groups over an 18-month period, entailing greater scale-up for groups receiving higher service levels at baseline, thus accounting for underlying structural barriers to healthcare access.

We assessed interventions individually and in all combinations (excluding any that would not practically be implemented jointly) for a total of 10,239 unique combinations. We assessed these combinations at optimistic implementation levels, where HIV testing and ART engagement and re-engagement interventions were delivered at the upper bound of publicly-documented evidence of scale-up [28].

Regarding the selected HIV prevention interventions, first, we defined optimistic expansion of SSP in accordance with the World Health Organization's (WHO) definition of high coverage [29], (200 syringes per PWID per year) with the exception of Seattle (Table 2). Second, we considered scaled-up access to methadone and buprenorphine individually given the different constraints on each modality in the US [30]. We defined the optimistic expansion of MOUD as 40% coverage of treatment with buprenorphine among PWID with an opioid use disorder to reach WHO guidelines on high coverage [29]. Optimistic expansion of MOUD with methadone was derived from the highest annual growth among PWID across the six cities [7, 28], thus reaching 40%-55% total MOUD coverage across cities. In addition to reducing the number of injections (and therefore shared injections) [31], MOUD decreased the probability of ART discontinuation [32], improved the quality of life [33] and reduced the risk of mortality [34]. Finally, given the uncertainty about PrEP uptake among PWID [35], we assumed no coverage in the status quo and that optimistic expanded access would result in 50% coverage among PWID and MSMWID. The methods and data sources we used to estimate the scale of delivery and the costs of implementing, delivering and sustaining each intervention were previously described elsewhere [7, 19, 28].

Economic analysis

We used a healthcare sector perspective to calculate incremental costs (2018 USD) and quality-adjusted life-years (QALYs) for the entire adult population in each city associated with the implementation of evidence-based interventions targeted exclusively to PWID. Interventions were sustained for a period of 10 years to match the goals of the 'Ending the HIV Epidemic' initiative with outcomes evaluated over 20 years to capture long-term individual health benefits and 2nd-order transmission effects (i.e., prevented cases beyond those directly reached by the interventions). We adhered to best-practice guidelines for health economic evaluation and both costs and QALYs were reported using a 3% annual discount rate [36, 37]. Model-projected

outcomes also included new HIV infections averted and we reported reduction in incidence among PWID over a 10-year period.

In addition, we estimated health production functions, representing combination implementation strategies providing the greatest health benefits for a range of investment levels, incremental to the status quo. We followed methodological conventions [38] to estimate incremental cost-effectiveness ratios (ICERs) as the incremental cost per QALY gained for successive optimal combination implementation strategies along the health production function, compared to the next most costly strategy. We identified the strategy producing the greatest health benefits while still remaining cost-effective (highly cost-effective: ICER ≤1x per capita Gross Domestic Product; cost-effective: ICER >1, ≤3x per capita Gross Domestic Product) [37].

Sensitivity analysis

We performed probabilistic sensitivity analysis (using the 2,000 best-fitting calibrated parameter sets for each city) on individual interventions and the strategies producing the greatest health benefits while still remaining cost-effective to evaluate the extent of parameter uncertainty. Furthermore, using the selected combination for each city, we assessed the impact on incidence of an ideal implementation scenario, whereby each intervention reached 90% of its target population (Table 2).

We also conducted a scenario sensitivity analysis examining the impact of the changing opioid epidemic in two ways. First, we assumed a 40% increase in the PWID population with an opioid use disorder based on the projections of opioid injection prevalence from Chen et al. (2019) [39]. Second, we accounted for increased mortality risk from the introduction of fentanyl into the illicit drug supply for PWID who were not receiving MOUD by adjusting mortality estimates for each city using state-level evidence of law enforcement encounters testing positive for fentanyl (full

details are presented in the supplement) [40]. Finally, we considered in a separate scenario sensitivity analysis the impact of free PrEP provision (i.e., zero PrEP medication costs), in response to recent announcements to this end [41].

RESULTS

Combination Implementation Strategies

Combination implementation strategies producing the greatest health benefits while remaining cost-effective included between six (Atlanta and Seattle) and twelve (Miami) individual interventions (Figures 1 & 2). Among the five different combinations (Baltimore and New York City had the same set of interventions), care coordination to improve ART engagement and RAPID ART were not included in any city's optimal strategy while expanded access to MOUD (with buprenorphine and methadone) and rapid HIV testing integrated with MOUD were included across all cities. Additional scale-up of SSP was only recommended in cities with lower current syringe distribution levels (highly cost-effective in Atlanta and Los Angeles and cost-saving in Miami), and PrEP for PWID was only included in Miami's optimal strategy (full results in the supplement).

These strategies were estimated to produce QALY gains of between 5,914 [95% credible interval: 3,791–8,312] in Seattle and 25,615 [17,729–35,736] in New York City, over the 20-year study horizon. We estimated the selected strategies could reduce HIV incidence by between 8.1% [2.8%–13.2%] (Seattle) to 54.4% [37.6%–73.9%] (Miami) by 2030 (Figure 3). Implementing the selected combination strategies at near-ideal levels would result in large reductions in Miami, Los Angeles and Atlanta (75.5%, 49.0% and 44.8% respectively) and Baltimore, New York City and Seattle reaching 16.1%, 17.7% and 19.2% reductions, respectively (Figure 3).

Effects of Individual Interventions

Expanding integrated rapid testing with receipt of MOUD was found to be cost-saving in Baltimore, Los Angeles and Miami, and highly cost-effective in all other cities (Supplemental Table 1). Both the electronic medical records HIV testing reminder and nurse-initiated rapid HIV testing interventions were cost-saving in Baltimore and Miami, and they were either very cost-effective or cost-effective in every other city with the exception of Seattle. Interventions designed to

189 improve ART engagement and re-engagement provided greater value within each city compared
190 to ART initiation interventions. Among these interventions, ART re-linkage provided the most
191 value in Atlanta, Los Angeles and Miami, targeted ART retention in Baltimore and New York City,
192 and ART re-initiation in Seattle. Finally, the ART initiation intervention was only cost-effective in
193 Miami and New York City.

194 *Sensitivity Analysis*

195 The changing opioid epidemic scenario had a profound impact on the projections and the
196 increased mortality among PWID living with HIV resulted in 2030 incidence in the status quo that
197 was now projected to be lower by 6.1% (Miami) to 19.6% (Baltimore). As a result of the lower
198 prevalence of PWID living with HIV, strategies producing the greatest health benefits while
199 remaining cost-effective achieved more modest incidence reductions, ranging from 8.7% in
200 Baltimore to 31.6% in Miami. Strategies for Baltimore, Los Angeles, New York City and Seattle
201 included the same set of interventions, whereas expansion of SSP in Atlanta and PrEP in Miami
202 were no longer included despite remaining cost-effective when evaluated individually. Finally, the
203 provision of free PrEP resulted in incidence reductions that now ranged from 33.4% in New York
204 City to 52.2% in Los Angeles–Miami remained unchanged at 54.4% (Figure 3 & full results in the
205 supplement).

DISCUSSION

Results from this simulation study of six US cities with diverse microepidemics suggests that distinct combinations of evidence-based interventions targeted to PWID were required to produce the greatest public health impact in each setting. In no city would the combination that maximized health benefits while remaining cost-effective according to international standards completely eliminate new HIV infections among PWID. Nevertheless, optimistic expansion of targeted, locally-oriented strategies could achieve greater decreases in the burden of HIV in cities with relatively higher rates of new infections, reducing HIV incidence among PWID from 29.4% in Atlanta to 54.4% in Miami by 2030. In addition, these combinations could prevent resurgence in cities that have maintained low levels of HIV incidence among PWID and result in incidence below one new HIV infection per 1,000 PWID in Baltimore, New York City and Seattle.

Opioid-related harms continue to be a major public health concern in the United States. In addition to improving ART retention and reducing mortality and risk behaviors associated with transmission of HIV, the immediate and life-long improvements in the quality of life from expanded access to MOUD has the potential to provide considerably more health benefits (measured in QALYs) to PWID than any other intervention. Whereas there are clear similarities between New York City and Baltimore–earlier epicenters of the epidemic among PWID driven by opioids–and cities like Miami, Los Angeles and Seattle–featuring more injection of stimulants–our findings suggested that the substantial value provided by expanded access to MOUD was robust in the context of different settings with respect to injection drug use. Practical considerations often determine medication selection and important access barriers to MOUD persist despite a growing interest in expanding its availability to a broader range of settings [30, 42]. For instance, both New York City and Seattle have implemented low threshold programs that integrate access to MOUD with buprenorphine with SSP services. Still, nationally representative estimates for receipt of MOUD among PWID living with HIV have recently been noted to be as low as 8% [43]. With one

in four American with an opioid use disorder receiving any care and less than a third of those in care receiving MOUD, access to evidence-based treatment has not kept pace with the increasing problems associated with the opioid epidemic in the United States [44, 45].

There has been a strong consensus among communities of injection drug users (and the scientific community) that the implementation of PrEP for PWID should only be considered together with widespread access to comprehensive, low-threshold HIV prevention and care [35, 46]. In agreement with prior US-based modelling studies [12, 14], our results indicate that the large incremental costs and modest additional health benefits of expanding PrEP among PWID across cities (e.g., clusters on the right in Figure 1) did not provide sufficient value at current prices to be included in each distinct strategy. Miami offers an important counterexample. With an HIV epidemic featuring relatively higher transmission rates among men who have sex with men, PrEP provided a comparatively greater public health benefit than in other cities. Furthermore, the expansion of SSP services in Miami resulted in important cost savings that offset a large portion of the PrEP expansion costs in the chosen health- maximizing strategy. Naturally, there is the potential to achieve greater reductions in HIV incidence when PWID have access to PrEP, as highlighted by our free PrEP sensitivity analysis. Potential price reductions from generics or following the recent approval of a new PrEP formulation by the US Food and Drug Administration [47] may offer opportunities to improve the cost-effectiveness of providing PrEP to PWID. Nevertheless, using PrEP remains an individual choice, with adherence greatly determining its efficacy. Access to this biomedical intervention needs to be considered in the context of criminalization of persons who use drugs and structural barriers to HIV prevention and care that could potentially diminish the effectiveness of PrEP among PWID. Additionally, it is important to emphasize in the context of recommendations to offer PrEP to all persons at high risk of HIV acquisition [15] that a large proportion of PWID living with HIV have yet to fully benefit from ART as treatment and prevention [43].

Recent trends in the diagnosis of PWID living with HIV have shown promise [48] yet ART engagement among those diagnosed has stalled [43, 48]. Sustained viral suppression is necessary for reducing HIV transmission risk [49], and as our analysis suggests, additional funding to improve ART engagement among PWID and to re-engage those who have discontinued treatment may be well-justified across most settings. These findings were consistent with previous studies noting poorer retention [50], lower probability of ART initiation [51] and re-initiation that varied across geographic regions [26] and lower rates of viral suppression for PWID relative to non-PWID [43]. There have been promising examples of reducing disparities in viral suppression rates [52]. Nonetheless, multidimensional public health strategies addressing stigma and broader social determinants of health such as the lack of fulfillment of basic needs (food, housing, education) will be necessary to achieve and maintain undetectable viral loads among the most vulnerable communities, and ultimately stop the spread of HIV.

Finally, given low levels of testing among PWID [53], our analysis indicates that expanding HIV testing and integrating routine screening with prevention services can provide great value. Our findings suggest these interventions may even result in cost savings, owing to the relatively low cost of testing, and benefits of early detection and treatment [54], compared to the lifetime costs of HIV infection.

We have previously outlined limitations in the structure of the model and its evidence base [7, 19]. Our analysis had other limitations. First, our model was calibrated and validated using historical data and may not capture changing HIV outbreaks among PWID that are most likely indicative of emerging patterns of drug use, vulnerability, and injection behavior [55, 56]. Our sensitivity analysis on the changing opioid epidemic allowed us to assess the robustness of our results when accounting for both changing injection drug use prevalence and associated risks. Second, we did not explicitly account for the variation in injection frequency or sexual risk networks among subgroups using different substances [57]. Nonetheless, we accounted for average behavior

among all PWID and conducted probabilistic sensitivity analysis on all relevant parameters, determining the value of different strategies at the population level. Third, the selection of evidence-based interventions and data to inform scale-up implementation was not always specific to PWID; however, we used the best publicly-available evidence and provided rankings on the quality of the evidence used [28]. Lastly, we only captured HIV prevention benefits from SSP. Incorporating broader health benefits from HCV and overdose prevention would likely result in assessments of greater value even for well-resourced cities.

In conclusion, evidence-based interventions targeted to PWID can deliver considerable value, however ending the HIV epidemic among PWID will require innovative implementation strategies and supporting programs to reduce social and structural barriers to care.

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Conflict of Interests

EK, XZ, BE, JEM, CNB, CDR, DJF, KAG, BDLM, SHM, LRM, AP, BRS, SAS and BN declare no competing interests. JCD has participated in research supported by grants to the University of Washington from Hologic.

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Contributors. EK and BN conceptualized the study and wrote the first draft. EK and XZ conducted analyses. EK, XZ and BE contributed to the evidence synthesis. BE contributed to manuscript development. EK, XZ, BE, JEM, CNB, CDR, JCD, DJF, KAG, BDLM, SHM, LRM, AP, BRS, SAS, and BN aided in the interpretation of results and provided critical revisions to the manuscript. BN secured funding for the study. All authors approved the final draft.

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Table 1. HIV among persons who inject drugs† in 2017 and selected HIV treatment and prevention service levels in 2015 in our six cities.

	Atlanta, GA	Baltimore, MD	Los Angeles, CA	Miami, FL	New York City, NY	Seattle, WA
Persons who inject drugs that are living with HIV (% among all living with HIV)†						
Prevalence	3,612 (11.3%)	4,759 (21.3%)	5,575 (10.8%)	2,425 (9.3%)	13,037 (10.5%)	884 (12.9%)
New diagnoses*	67 (4.1%)	50 (11.4%)	146 (7.5%)	27 (2.3%)	64 (3.0%)	17 (10.8%)
HIV Prevention program service levels						
Estimated annual number of syringes distributed per PWID	2	20	19	6	24	196
Coverage of medication for opioid use disorder among PWID‖	3.0%	9.4%	15.7%	7.1%	19.9%	11.9%
HIV Testing levels among PWID / MSMWID^						
Proportion receiving an HIV test in the past year	30% / 15%	11% / 12%	40% / 25%	16% / 15%	9% / 41%	43% / 51%
HIV treatment engagement among PWID / MSMWID^						
Proportion of diagnosed initiating ART^^	44% / 38%	55% / 47%	51% / 44%	48% / 41%	39% / 42%	51% / 46%
Proportion discontinuing ART^^	28% / 25%	11% / 8%	14% / 13%	24% / 21%	11% / 8%	5% / 4%
Proportion re-initiating ART^^	42% / 44%	28% / 29%	23% / 20%	43% / 46%	31% / 32%	49% / 50%

PWID: Persons who inject drugs; MSMWID: Men who have sex with men who inject drugs; ART: Antiretroviral therapy.

† Persons who inject drugs include men who have sex with men who inject drugs.

* New diagnoses are from 2017 in city surveillance reports, except for Los Angeles were new diagnoses are for 2016, or from the Centers for Disease Control and Prevention's Surveillance HIV Surveillance Supplemental Report.

‖ Coverage is among the 72.7% of PWID estimated to have an opioid use disorder [24].

^ While the model runs in monthly cycles, we have converted these figures to yearly probabilities for ease of interpretation.

^^ ART initiation rates were estimated from the HIV Research Network (HIVRN) data, and ART discontinuation and re-initiation rates were estimated by a continuous-time multi-state Markov model based on the same HIVRN data [26].

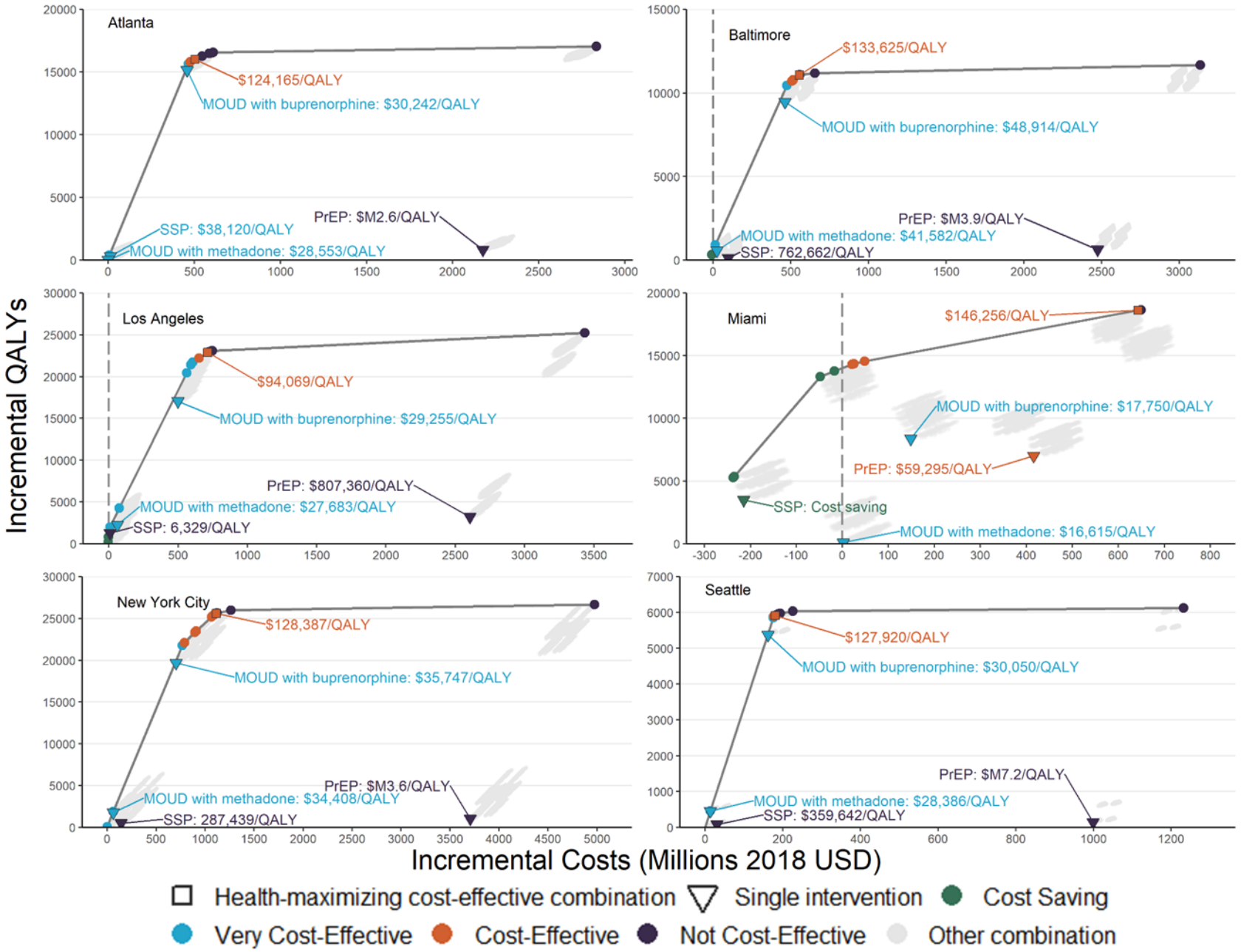
Counties included in city boundaries for Atlanta, Baltimore, Los Angeles, and Miami match those included in the definition of Ryan White Eligible Metropolitan Area (EMA) or Transitional Grant Area (TGA) while New York City and Seattle boundaries are restricted to a subset of counties. Counties included in each city are found in brackets: Atlanta (Barrow, Bartow, Carroll, Cherokee, Clayton, Cobb, Coweta, DeKalb, Douglas, Fayette, Forsyth, Fulton, Gwinnett, Henry, Newton, Paulding, Pickens, Rockdale, Spalding, Walton); Baltimore (Anne Arundel, Baltimore City, Baltimore County, Carroll, Harford, Howard, Queen Anne's); Los Angeles (Los Angeles county); Miami (Miami-Dade county); New York City (county with borough in brackets: New York [Manhattan], Kings [Brooklyn], Queens [Queens], Bronx [Bronx], Richmond [Staten Island]); Seattle (King county). Excluded counties for New York City compared to the Ryan White EMA definition included Westchester, Rockland and Putnam, and excluded counties for Seattle compared to Ryan White TGA definition included Snohomish and Island.

Table 2. Description, effectiveness and scale-up implementation scenarios for the evidence-based HIV prevention programs and care interventions included in our analysis.

Intervention	Supporting evidence			Description and effectiveness**	Scale-up implementation scenarios†	
	Source [Evidence Level*]	Study Design	Study Setting		Optimistic	Ideal^
HIV prevention programs						
Syringe service programs (SSP)	Aspinall et al. 2014 Int J Epi [2a]	Meta-analysis	SSP	Clean injection equipment reduces the risk of parenteral HIV transmission by 58%.	200 syringes / PWID / year ‡	90%
MOUD with buprenorphine	MacArthur et al. 2012 BMJ [2a]	Meta-analysis	Primary Care & OTP	Office-based MOUD reduces the number of shared injections by 54% for PWID with OUD.§	29% #	90% ##
MOUD with methadone	MacArthur et al. 2012 BMJ [2a]	Meta-analysis	Primary Care & OTP	Opioid treatment program-based MOUD reduces the number of shared injections by 54% for PWID with OUD.§	Additional scale-up of 23%	90% ##
Full-time PrEP	Liu et al. 2016 JAMA Intern Med	RCT substudy & Cohort study	Primary Care	Protective level adherence to PrEP (≥4 doses/week) reduces the risk of HIV infection by 60%.Ŧ	50%	90%
HIV Testing						
EMR testing offer reminder	Felsen et al. 2017 JAIDS [2b]	Quasi-exp. pre/post	Hospital	HIV testing increases by 178% among among PWID visiting the ER.	13%-35%	14%-36% ^^
Nurse-initiated rapid testing	Anaya et al. 2008 J Gen Intern Med [2b]	RCT	Primary Care	Nurse-initiated screening and rapid testing increases HIV testing by 73% during health care visits.	34%-52%	56%-87%
MOUD integrated rapid testing	Metsch et al. 2012 Am J Pub H [1b]	RCT	DTP	On-site rapid testing increases HIV testing by 352% among PWID receiving MOUD.	22%	49%
ART engagement						
Case management (ARTAS)	Gardner et al. 2005 AIDS [1b]	RCT	HIV clinics	Contacts with a case manager increases ART initiation by 41% among PLHIV linked to care.	61%	77%
Care coordination	Robertson et al. 2018 Am J Epi [2b]	Pre/post ‖	HIV clinics	Comprehensive care coordination increases ART retention by 10% among PLHIV.	12%-25%	34%-68%
Targeted care coordination	Robertson et al. 2018 Am J Epi [2b]	Pre/post ‖	HIV clinics	Targeted comprehensive care coordination increases ART retention by 32% among PLHIV with CD4<200 cells per µL.	41%-48%	57%-66%
EMR ART engagement reminder	Robbins et al. 2012 Ann Int Med [1b]	RCT	HIV clinics	Interactive EMR alerts reduces ART drop-out by 31% among PLHIV on ART.	47%-84%	60%-91% ^^
RAPID ART initiation	Pilcher et al. 2017 JAIDS [3b]	Cohort study	HIV clinics	Multidisciplinary care and support increases immediate ART initiation by 32% among newly diagnosed PLHIV.	38%-71%	47%-90%
ART re-engagement						
Enhanced personal contact	Gardner et al. 2014 Clin Infect Dis [1b]	RCT	HIV clinics	Continuous contact increases ART re-initiation by 22% among PLHIV having dropped-out of ART.	49%	62%
Re-linkage program	Bove et al. 2015 JAIDS [2b]	Cohort study	HIV clinics	Outreach using surveillance data increases ART re-initiation by 70% among PLHIV who are out-of-care.	10%	22%

PWID: Pepople who inject drugs; OUD: opioid use disorder; MOUD: Medication for OUD; PrEP: Pre-exposure prophylaxis; EMR: Electronic medical records;
ER: Hospital emergency room; PLHIV: People living with HIV; RAPID: Rapid ART Program for Individuals with an HIV Diagnosis; RCT: Randomized control trial.
* Levels of evidence adapted from Oxford Centre for Evidence-based Medicine – Levels of Evidence: 1a - Systematic review of RCTs; 1b - Individual high-quality RCT; 2a - Systematic review of cohort studies; 2b - Individual cohort study or quasi-experimental study; 3a - Systematic review of case-control studies; 3b - Individual case-control study; 4 - Case series.
** Interventions target the PWID adult population 15-64 including men who have sex with men who inject drugs.
^ Ideal implementation refers to 90% adoption unless otherwise noted by ^^ which refers to 100% adoption of EMR.
§ MOUD also reduces the risk of mortality, increases quality of life, and decreases the probability of ART discontinuation.
† Where applicable, scale-up ranges indicate evidence stratified by sex/gender and/or race/ethnicity and/or city/region.
‡ As recommended by the World Health Organization (WHO) [29], except Seattle (400 syringes / PWID / year) since status quo service levels were already equivalent to this level.
# As recommended by the World Health Organization (WHO) [29], 40% coverage among the 72.7% of PWID with an OUD [26] results in 29% coverage among all PWID.
Maximum 90% coverage of both medications combined among the 72.7% of PWID with an OUD [26].
Ŧ Effectiveness defined as efficacy for 4 doses/week [96% (90%, 99%)] X protective level adherence [62.5% (associated with taking ≥4 doses/week)], further details in the supplement.
‖ Study with contemporaneous surveillance registry–based comparison group

Figure 1. City-level health production functions for evidence-based prevention and care interventions targeted to persons who inject drugs and men who have sex with men who inject drugs

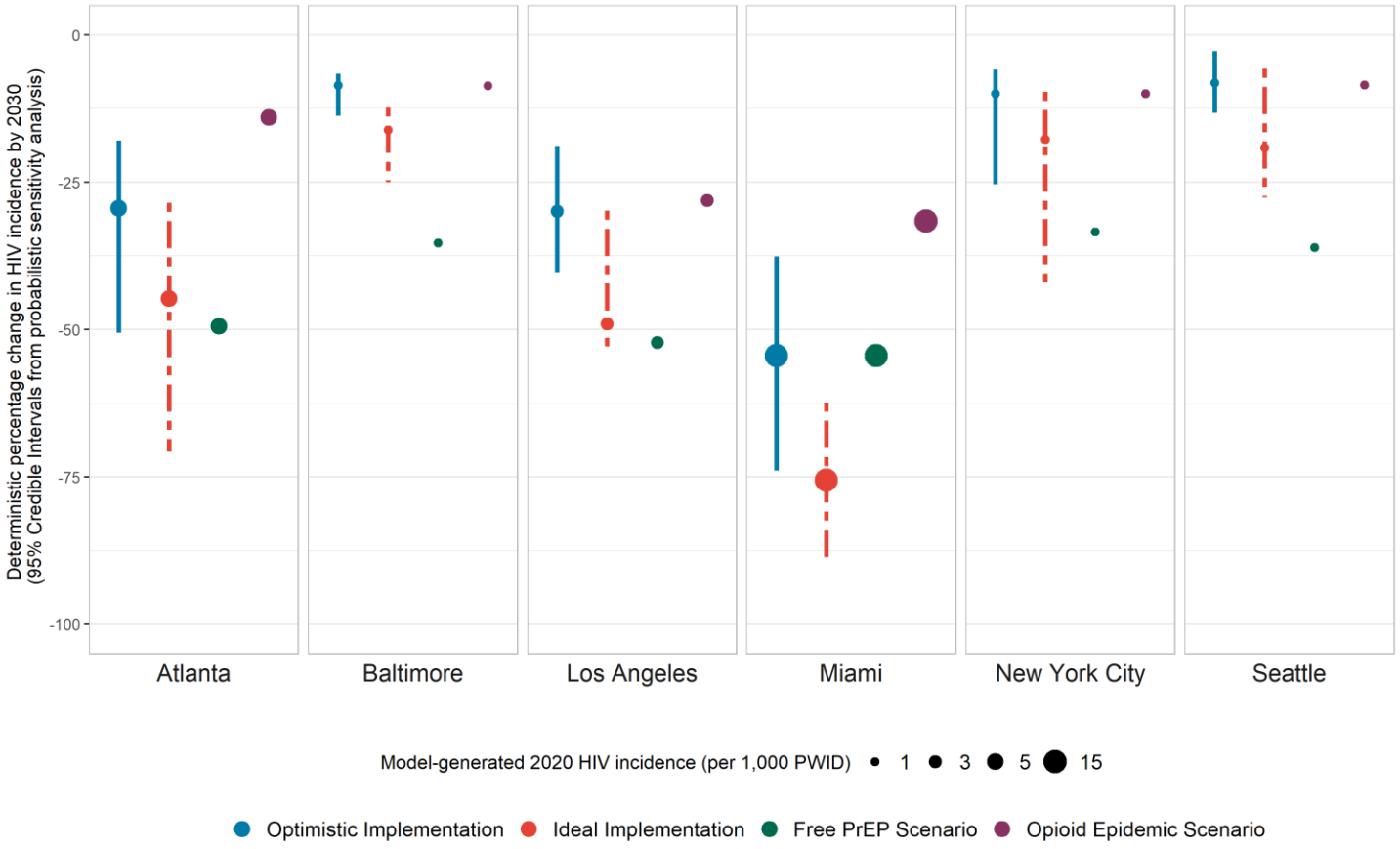


QALY: Quality-adjusted life-year; SSP: Syringe service programs; MOUD: Medication for opioid use disorder; PrEP: Pre-exposure prophylaxis.

Figure 2. Interventions included in the health-maximizing cost-effective combinations

PWID: Persons who inject drugs; MSMWID: Men who have sex with men who inject drugs; MOUD: Medication for opioid use disorder; PrEP: Pre-exposure prophylaxis; EMR: Electronic medical records; ART: Antiretroviral therapy.

Figure 3. Projected reductions in HIV incidence among persons who inject drugs and men who have sex with men who inject drugs



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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

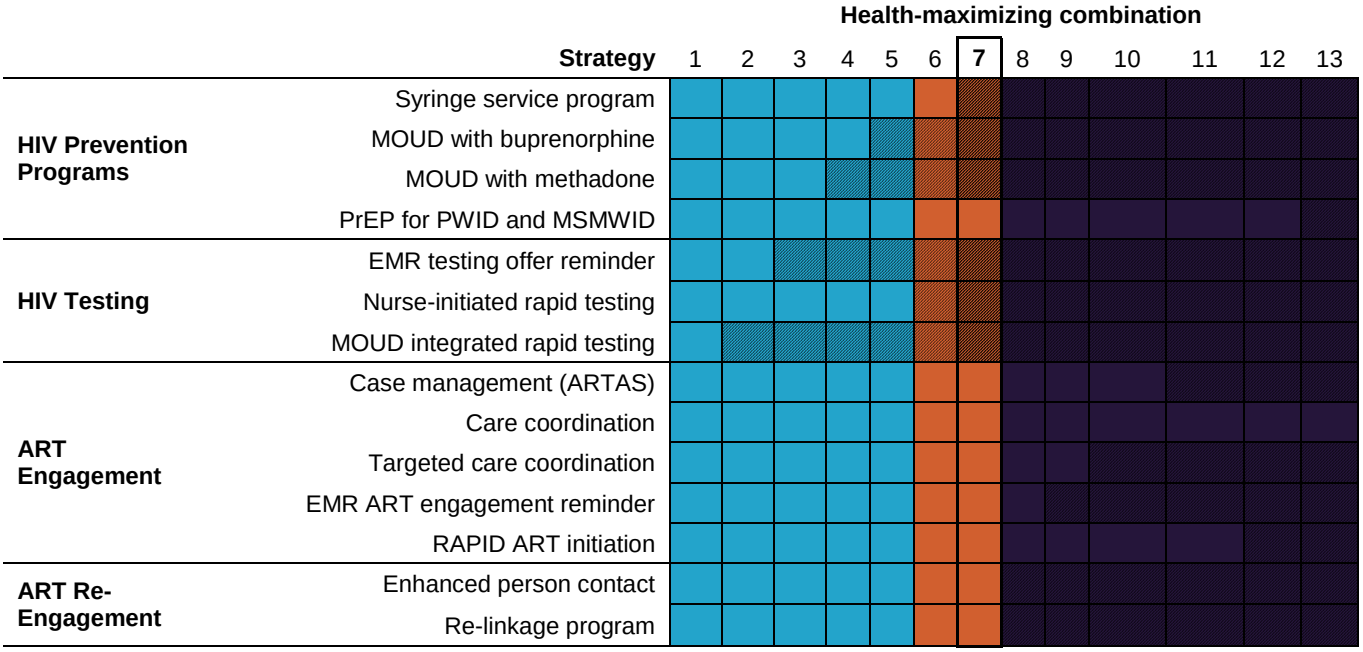
Atlanta

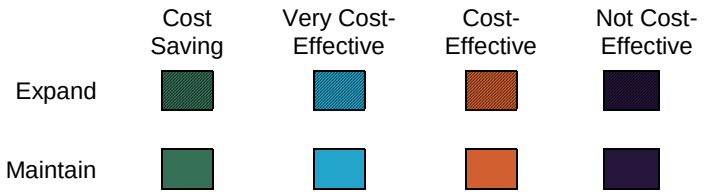
Strategy	*Incremental Cost: $M*	*Incremental QALYs*	*ICER: $ / QALY*
1	0.0	0	-
2	0.1	23	4,649
3	6.6	381	18,224
4	7.1	396	28,670
5	464.6	15,627	30,039
6	477.3	15,803	72,056
7	**503.3**	**16,013**	**124,165**
8	545.3	16,257	171,961
9	586.5	16,484	181,576
10	590.1	16,497	266,883
11	606.2	16,549	313,350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

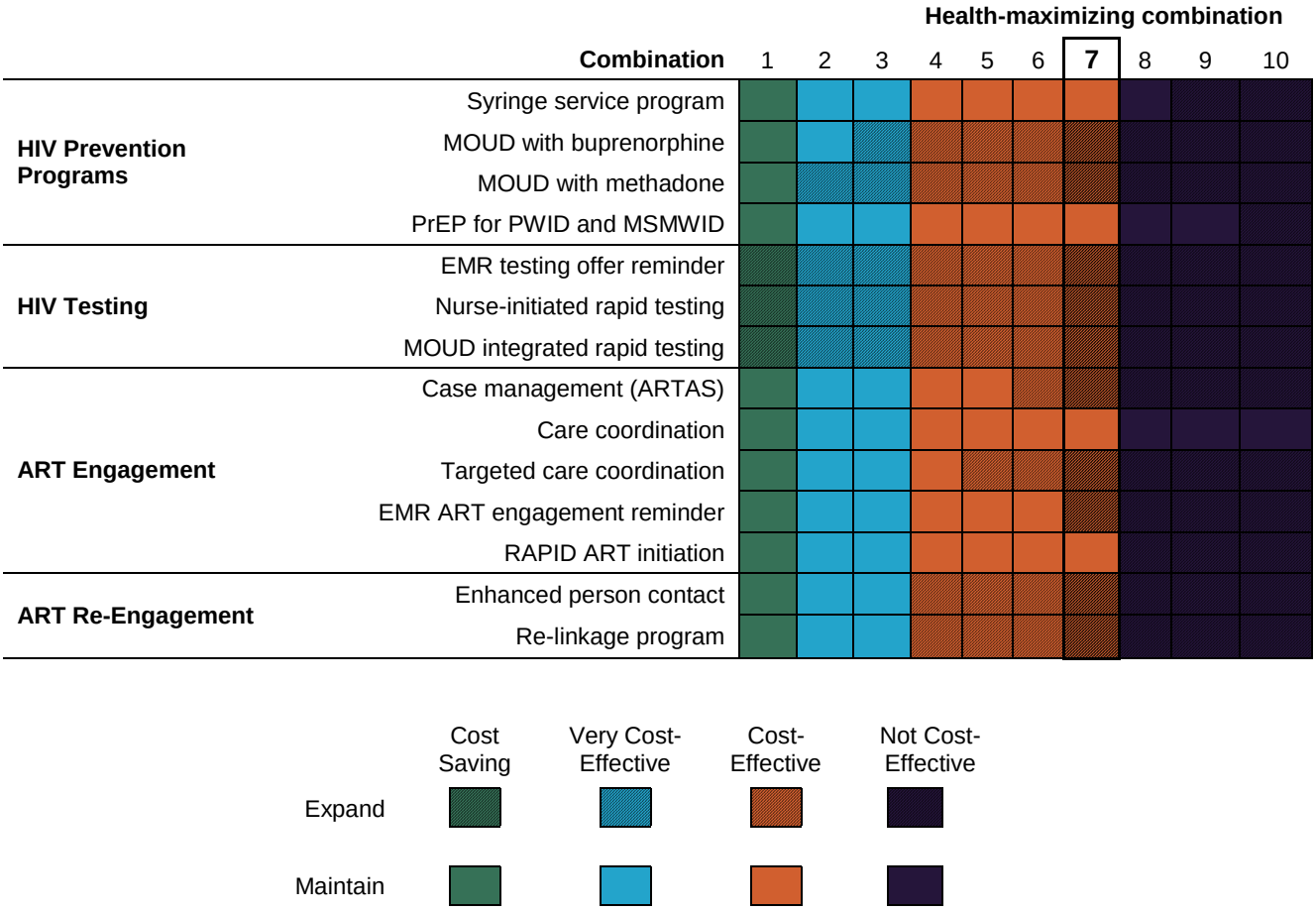
Baltimore

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

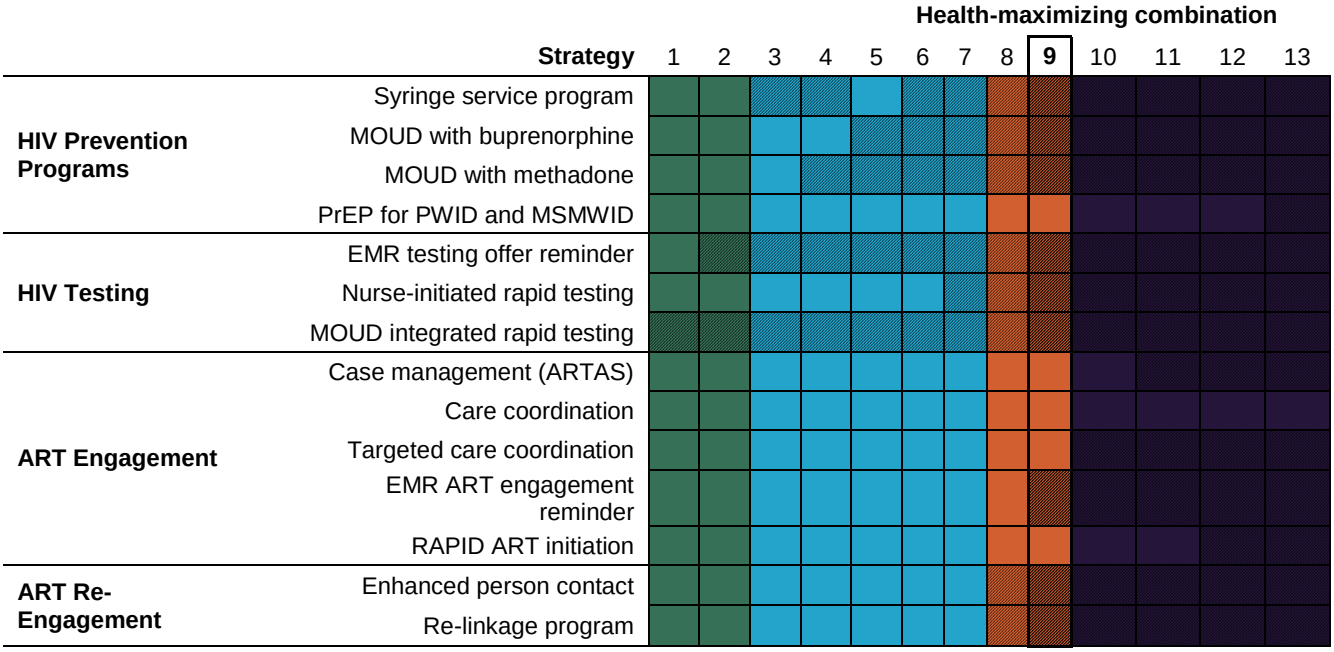
Los Angeles

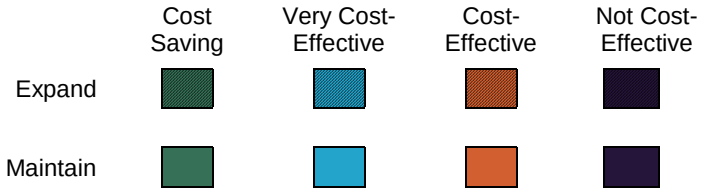
Strategy	*Incremental Cost: $M*	*Incremental QALYs*	*ICER: $ / QALY*
1	-3.8	201	CS
2	-2.6	811	CS
3	9.4	1,993	10,092
4	74.0	4,246	28,685
5	562.3	20,429	30,174
6	592.8	21,407	31,244
7	606.6	21,714	44,764
8	650.6	22,226	85,936
9	**714.0**	**22,900**	**94,069**
10	719.8	22,939	150,777
11	738.1	23,039	182,050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

† 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.

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

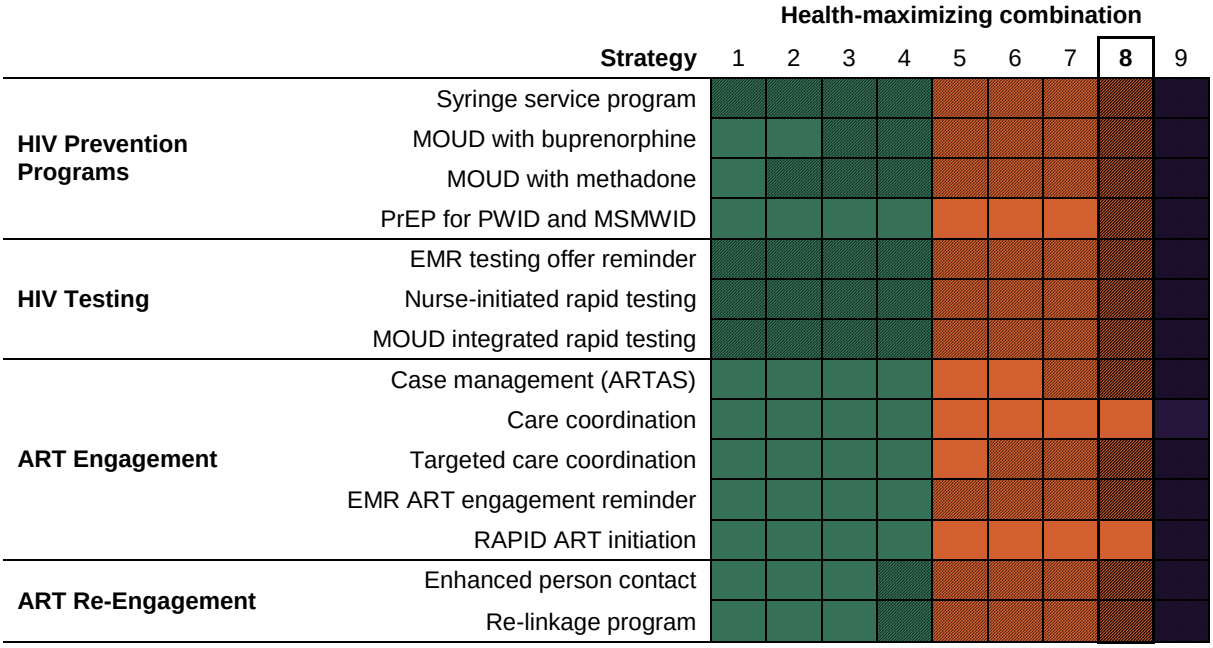
Miami

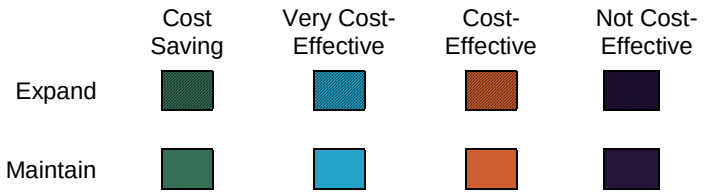
Strategy	*Incremental Cost: $M*	*Incremental QALYs*	*ICER: $ / QALY*
1	-237.2	5,273	CS
2	-235.1	5,367	CS
3	-48.1	13,314	CS
4	-17.2	13,773	CS
5	21.0	14,314	70,652
6	25.2	14,355	104,079
7	48.4	14,551	118,613
8	**643.3**	**18,618**	**146,256**
9	649.2	18,647	204,299

$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.

† 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.

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

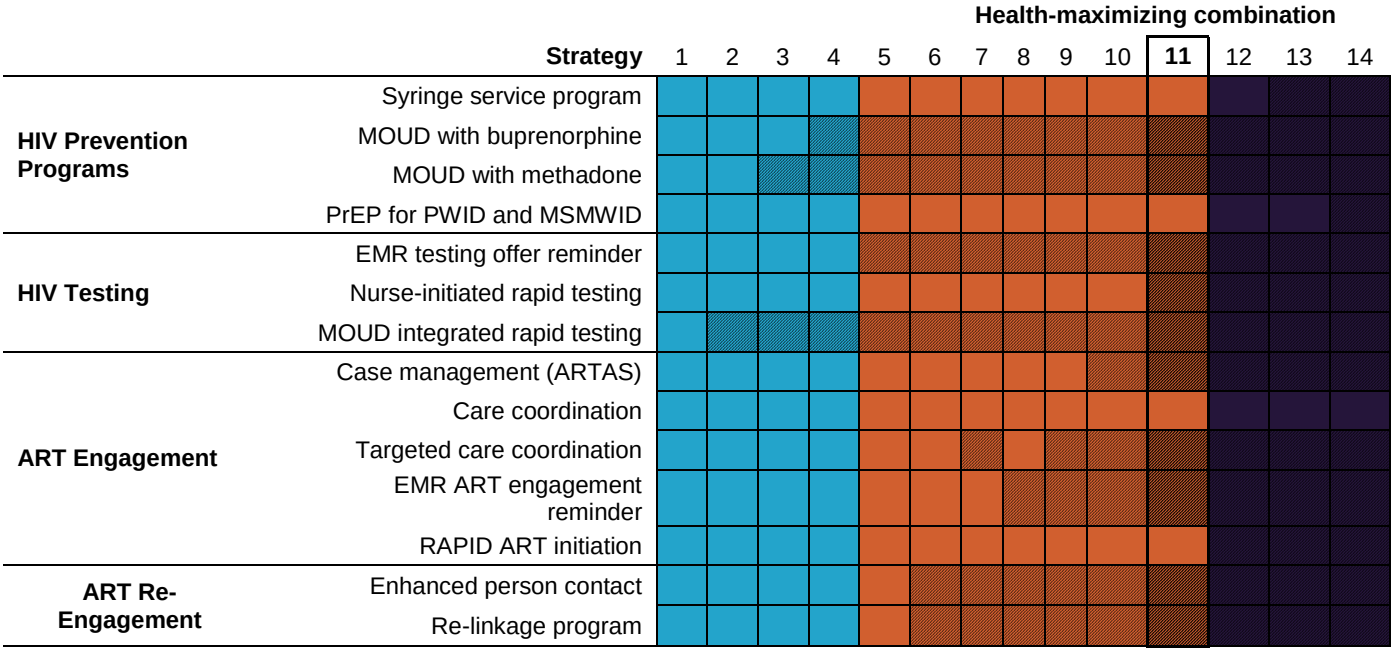
New York City

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

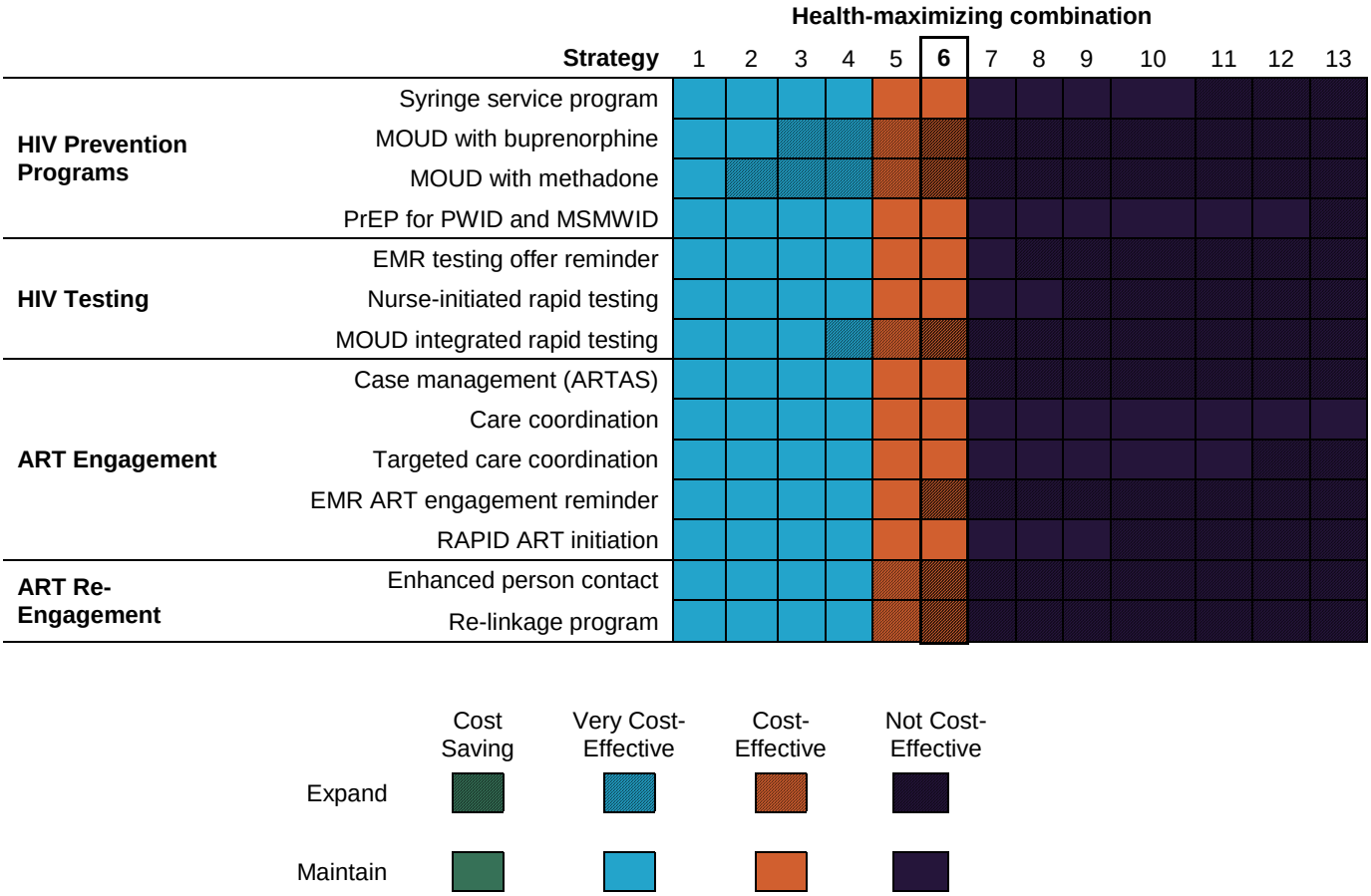
Seattle

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.

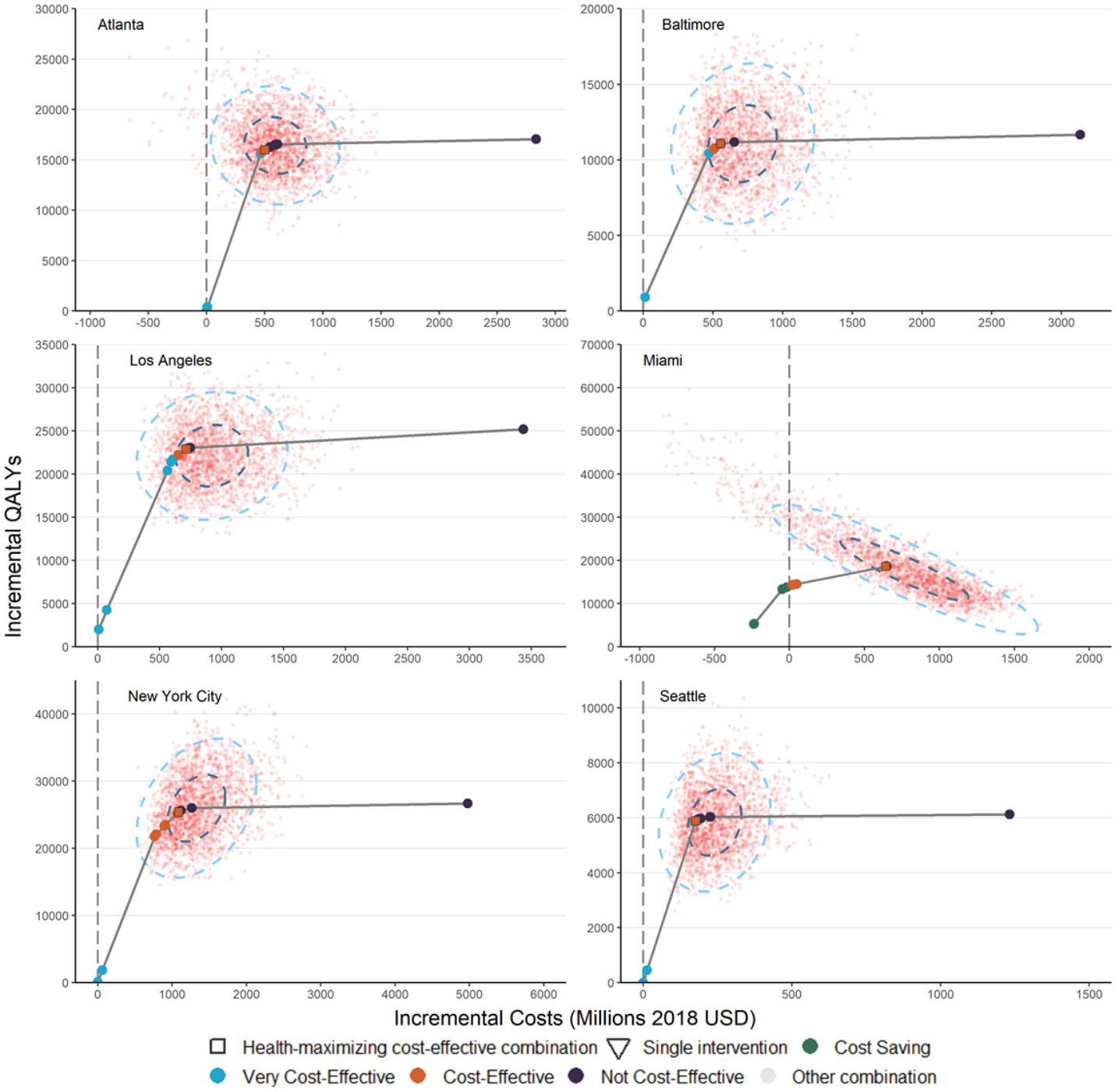
SEATTLE

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

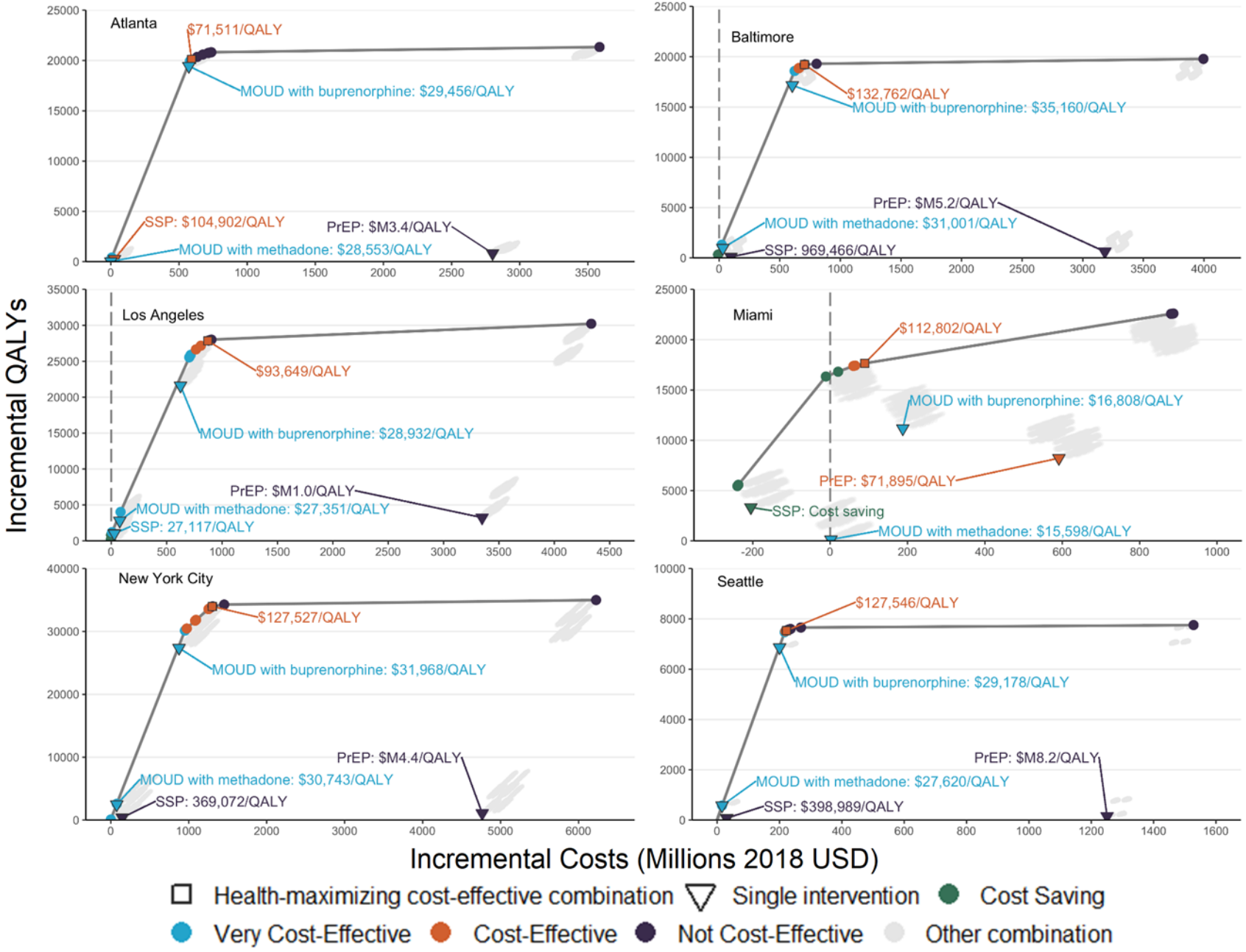
Intervention	Seattle		
HIV prevention programs	*ΔTC ($M)*	*ΔQALYs*	*ICER ($'000s)*
Syringe service program	29.8 [19.1 - 58.2]	83 [-5 - 109]	359.6 [CS - 7469.5]
MOUD with buprenorphine	161.5 [102.4 - 423.4]	5375 [3368 - 7649]	30.1 [19.7 - 81.7]
MOUD with methadone	12.9 [4.6 - 32.7]	455 [311 - 585]	28.4 [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.

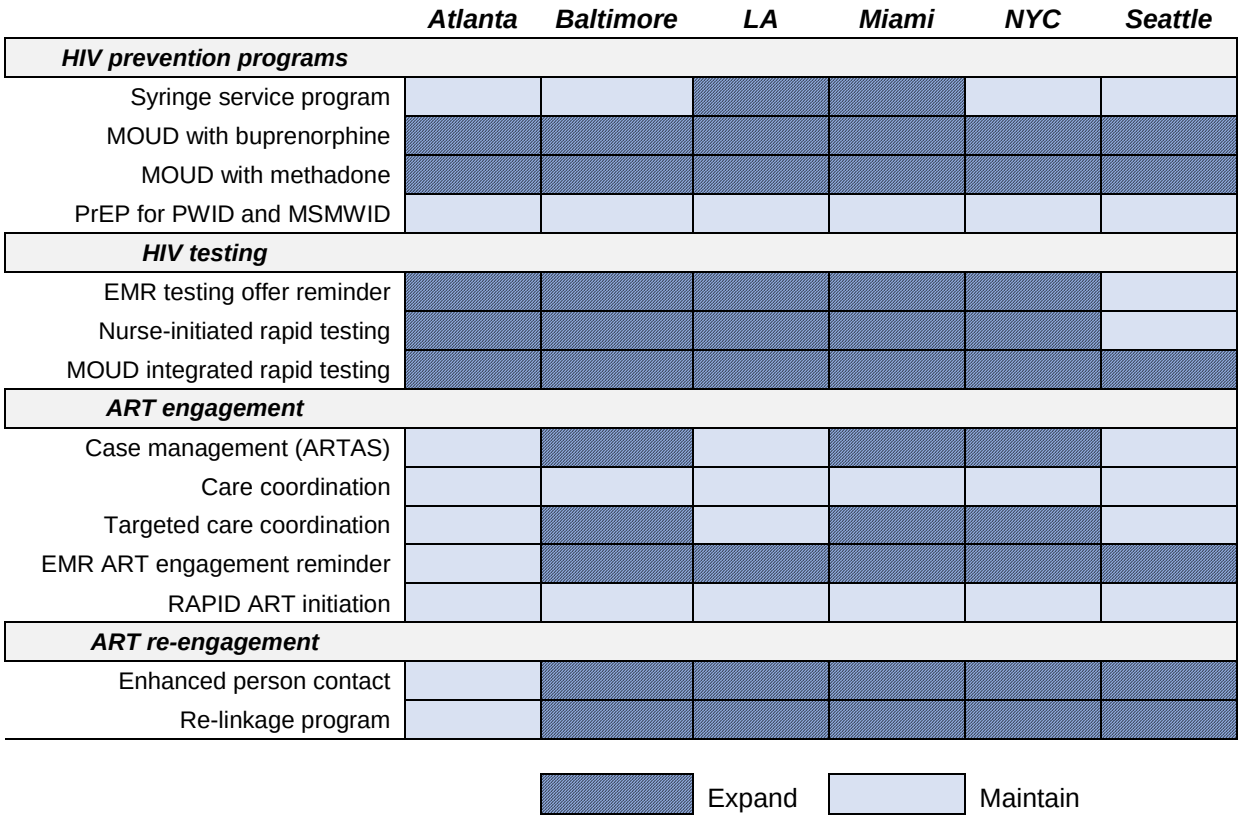
Supplemental Figure 1. Probabilistic sensitivity analysis displaying uncertainty surrounding optimal combination implementation strategies (with 50% and 95% uncertainty ellipses)



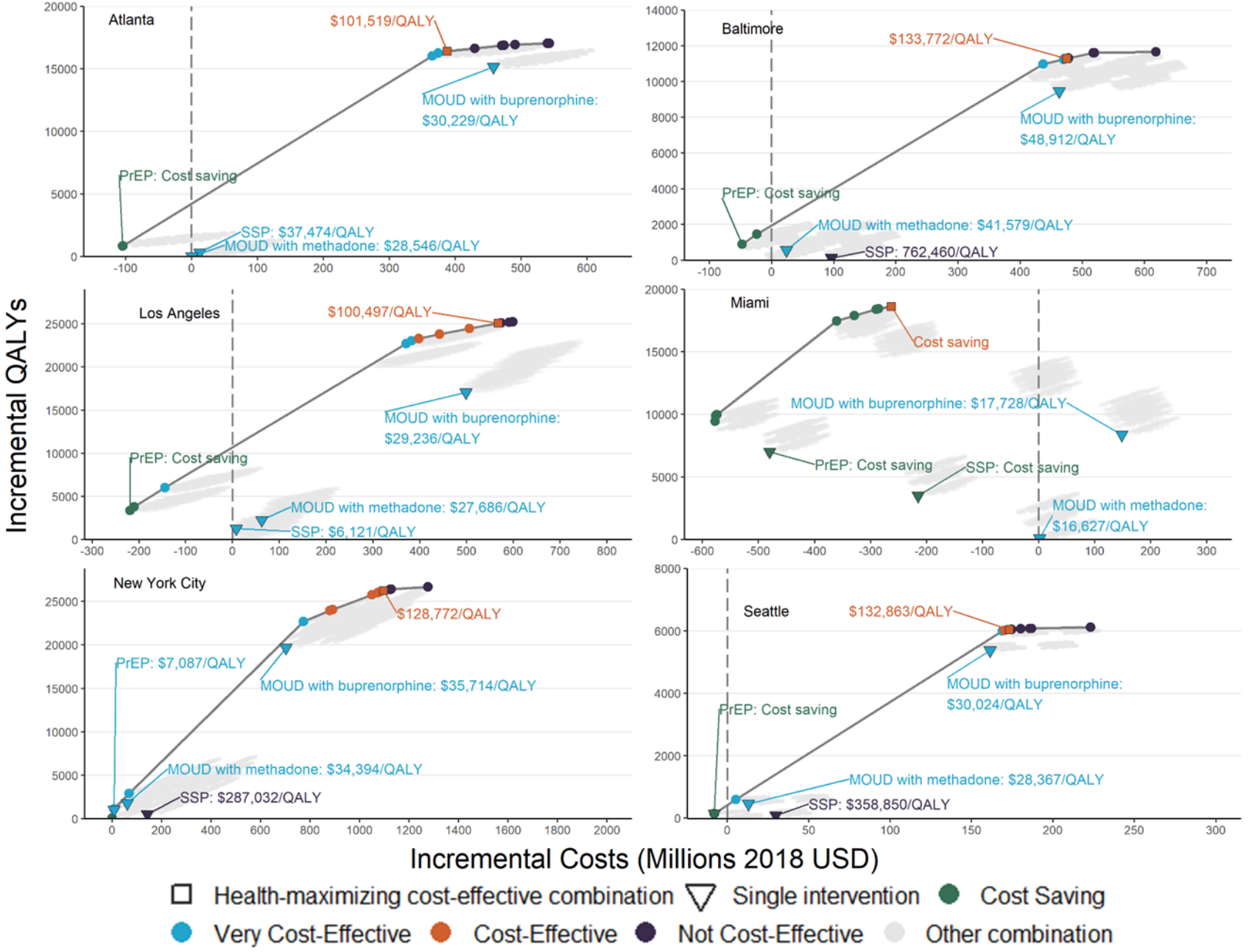
Supplement Figure 2. City-level health production functions for the changing opioid epidemic scenario



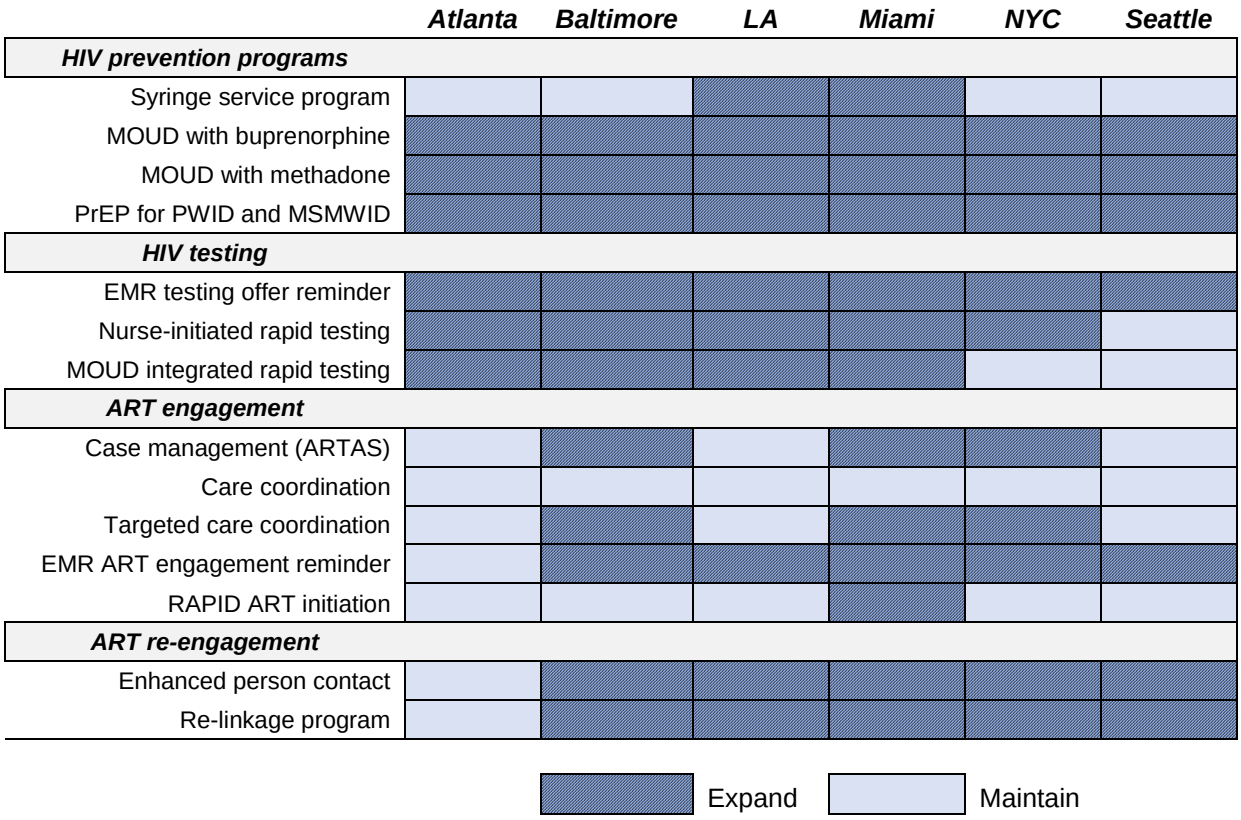
Supplement Figure 3. Interventions included in the health-maximizing cost-effective combinations for the changing opioid epidemic scenario



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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