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Cost-effectiveness of implementing HIV and HIV/syphilis dual testing among key populations in Viet Nam: a modeling analysis

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ABSTRACT

Objectives

Key populations, including sex workers, men who have sex with men, and people who inject drugs, have a high risk of HIV and sexually transmitted infections (STIs). We assessed the health and economic impacts of different HIV and syphilis testing strategies among three key populations in Viet Nam using a dual HIV/syphilis rapid diagnostic test (RDT).

Setting

We used the Spectrum AIDS Impact Model to simulate the HIV epidemic in key populations in Viet Nam and evaluated five testing scenarios. We used a 15-year time horizon and all costs are from the provider's perspective.

Participants

We include the entire population of Viet Nam in the model.

Interventions

We model five testing scenarios among key populations: 1) annual testing with an HIV rapid diagnostic test (RDT), 2) annual testing with a dual RDT, 3) biannual testing using dual RDT and HIV RDT, 4) biannual testing using HIV RDT, and 5) biannual testing using dual RDTs.

Primary and secondary outcome measures

The primary outcome is incremental cost-effectiveness ratios (ICERS). Secondary outcomes include HIV and syphilis cases and costs for each proposed intervention.

Results

Annual testing using a dual HIV/syphilis RDT was cost saving and averted 3,206 HIV cases and treated 7,719 syphilis cases compared to baseline over 15 years. Biannual testing using one dual test and one HIV RDT, or two dual tests both averted an additional 875 HIV cases and were cost-effective ($1,024 and $2,518 per DALY averted, respectively). Annual or biannual HIV testing using HIV RDTs and separate syphilis tests were more costly and less effective than using one or two dual RDTs.

Conclusions

Annual or biannual HIV and syphilis testing using dual RDTs among key populations can be cost-effective and support countries in reaching global reduction goals for HIV and syphilis.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Strength: Our model presents novel cost-effectiveness estimates for the use of dual HIV/syphilis testing in key populations that can inform health planners
- Strength: We include five testing scale up scenarios using both HIV RDT and dual HIV/syphilis RDT
- Strength: Our model is informed by demographic, behavioral, and biological data from government sources, surveys, surveillance, publicly available reports, databases, and peer-reviewed literature
- Limitation: We made some assumptions regarding the timing and uptake of HIV and syphilis testing among key populations that may be inaccurate.
- Limitation: Our model assumes that increased syphilis testing and treatment will not impact syphilis prevalence, however, it is unknown whether increased testing will reduce or increase syphilis prevalence.

INTRODUCTION

Key populations, including people who inject drugs (PWID), men who have sex with men (MSM), sex workers (SW), and transgender populations, are at higher risk of acquiring both HIV and syphilis. HIV incidence is significantly higher among key populations in all regions compared to the general population; however, differences vary substantially by region and by key population.[1] While key populations represent 25% of new HIV cases in sub-Saharan Africa, they represent 80% of new HIV cases in the rest of the world.[2] Recent data suggests syphilis incidence, while remaining prevalent in low- and middle-income countries (LMIC), is increasing among key populations, particularly MSM.[1, 3, 4] World Health Organization (WHO) HIV testing guidelines recommend HIV retesting at least annually for key populations and more frequent testing (3-6 months) for those with high ongoing risk.[5] WHO guidelines for syphilis screening depend on population and setting. Rapid diagnostic tests (RDTs) are increasingly being used to screen for syphilis in some settings, yet laboratory-based testing remains common,[6] leaving many key populations unreached by syphilis testing. With the introduction of prequalified dual HIV/syphilis RDTs, and the recent WHO recommendation to offer dual HIV/syphilis testing in antenatal care (ANC) settings,[7] it is important to consider how further integration and expansion of dual HIV/syphilis testing could benefit key populations.

Since 2015, WHO has recommended immediate initiation of antiretroviral therapy (ART) for all people living with HIV (PLHIV) [8] and the United Nations 95-95-95 targets aim to diagnose 95% of PLHIV, provide 95% of PLHIV with ART, and ensure 95% PLHIV on ART are virally suppressed.[9] Despite progress towards these goals – in 2019 81% of PLHIV knew their HIV status and 67% were on ART – this progress is uneven; only 2/3 of key populations are aware of their HIV status.[2] While key populations lag behind the general population in all phases of testing, linkage to treatment, and viral suppression, the largest gap exists in testing.[10] WHO has also developed a global strategy on sexually transmitted infections (STIs) which aims for a 90% reduction in syphilis incidence by 2030, and for 70% of key populations to have access to STI and HIV services, including prevention, testing, and treatment.[11] Increased syphilis testing and treatment may reduce syphilis burden among key and general populations, as well as HIV incidence since early symptomatic syphilis increases risks of HIV acquisition and transmission.[3] Currently, the frequency of syphilis testing recommended by WHO is based on local epidemics; however, the optimal frequency for syphilis testing among key populations is unknown.

In Viet Nam, the national HIV prevalence is <1% in the general population, and significantly higher in key populations, with prevalence ranging between 3-13% among PWID, MSM, and FSW. Similarly, syphilis prevalence among MSM (6.7%) and FSW (2.1%) are also higher than the general population (0.3%).[12] With budgetary constraints in HIV and STI programs, and the health sector, identifying cost-effective strategies for targeted HIV and syphilis testing among high risk groups in Viet Nam is crucial to inform policymakers seeking to optimize resource allocation to maximize population health. We modeled the health impacts and costs associated with varying frequencies of HIV and syphilis testing for key populations, using test scenarios that include a dual HIV/syphilis RDT.

METHODS

Settings and Populations

We modeled three key populations: MSM, PWID, and FSW (and their clients) in Viet Nam, using national level HIV prevalence and syphilis prevalence estimates for each key population **(Table 1)**.

Table 1. Model parameters for Spectrum input and cost-effectiveness analysis of HIV and syphilis testing scale up among key populations in Viet Nam. a = 2018 Viet Nam HIV Sentinel Surveillance. b = 2019 Viet Nam HIV Sentinel Surveillance. * = Spectrum model prior. ** = assumed. *** = Based on information from in-country source.

Model parameter	Value
HIV Prevalence	
MSM (incl. TGW)[a]	10.8%
PWID[b]	12.7%
FSW[a]	3.6%
Syphilis Prevalence[12]	
MSM (incl. TGW)	6.7%
PWID	0.3%
FSW	2.1%
Baseline syphilis test acceptance	
MSM (incl. TGW)[45],[46],[14]	27%
PWID[15]	16%
FSW[16],[47]	35%

Syphilis DALYs averted[48]	
DALYs averted per syphilis case treated	0.04
ART	
2019 Coverage***	70%
Annual Scale-Up**	4.8%
Transmission Reduction Efficacy*	70%
Mortality Reduction Efficacy*	80%
Other Prevention	
Condom Use**	50%
Condom Efficacy*	80%
PrEP Coverage (MSM incl. TGW)**	5%
PrEP Efficacy*	90%
PrEP Adherence*	80%
Costs***	
HIV Lay Test†	$4.50
Syphilis RPR†	$6.28
HIV/Syphilis Dual Test†	$6.50
ART‡	$285
Syphilis Treatment	$6.50
Time Horizon	2020 - 2035
Discount Rate	3%

124 † Testing costs include labor, incentives, travel costs, and test kits. Primary cost driver between tests is the cost of the test kit.
125 ‡ ART cost includes labor, laboratory monitoring costs, ARVs, and other recurring costs.
126 * MSM=men who have sex with men, FSW=female sex workers, PWID=people who inject drugs, TGW=transgender women,
127 ART=antiretroviral therapy, PrEP=pre-exposure prophylaxis, syphilis RPR=syphilis rapid plasma regain.

129 **Model**

130 We used a deterministic, compartmental model to simulate the HIV epidemic in key populations from 2020-2035
131 using the AIDS Impact Model within the Spectrum software package (v 5.76). The model estimates annual HIV
132 incidence, AIDS mortality, and disability. We simulated the impact of increasing HIV testing frequency using the
133 Goals model within Spectrum, as previously described.[13] Briefly, the model is age- and sex-stratified with
134 compartments for MSM, PWID, FSW and their clients, and low- and medium-risk heterosexuals.[1] The model was
135 parameterized with demographic, behavioral, and biological data from government sources, surveys, surveillance,
136 publicly available reports, databases, and peer-reviewed literature. To estimate syphilis burden, we used

[1] Low-risk heterosexuals are those in stable couples while medium-risk heterosexuals are those that engage in casual sex but are not in a high-risk group (high risk groups: MSM, FSW, PWID).

population size estimates from the Goals model and population-specific estimates of prevalence;[12] we estimate the number of persons tested positive and treated for syphilis infection under each scenario. This model assumes that syphilis testing and treatment does not impact syphilis prevalence. For both HIV and syphilis, disability-adjusted life years (DALYs) are calculated for each scenario. Model key parameters are shown in **Table 1**.

Costs

Cost inputs include cost per HIV test, initial syphilis test (rapid plasma reagin (RPR)), and the dual HIV/syphilis RDT. We used local data on the personnel, commodities, and transport costs associated with lay testing and estimate costs (**Table 1**). ART costs include personnel, commodities, clinical follow-up, and laboratory monitoring. This analysis includes the costs of intervention delivery and treatment (penicillin and ART) but does not consider additional averted sequelae costs such as the treatment of opportunistic infections due to uncontrolled HIV. All costs are from the provider's perspective and reported in 2019 US dollars.

Scenarios

Our baseline scenario estimates annual HIV testing based on current WHO recommendations,[5] and syphilis testing based on observed uptake. In the baseline scenario, we assume 50% of individuals in key populations test annually for HIV, and syphilis testing with RPR occurs at rates specific to each key population (**Table 2**).[14–16] We considered alternative scenarios with varying testing frequency and test type (separate HIV and syphilis RPR, or a combined dual syphilis/HIV RDT) among key populations from 2020 to 2035. Scenarios modeled include: **1)** annual HIV testing with RDT and baseline syphilis RPR testing, **2)** annual testing with dual RDT, **3)** biannual testing (2 times per year), first with dual RDT and then with HIV RDT, **4)** biannual HIV testing with RDT and baseline syphilis RPR testing, and **5)** biannual testing with dual RDT **(Table 2)**. We assumed 75% test acceptance for the first test in all scenarios except baseline, and 90% of those who accepted the first test would accept the second test in all scenarios that include biannual testing.

Table 2: HIV/syphilis testing scenarios among key populations in Viet Nam. The table cells show the proportion of key populations in Viet Nam that receive each test per year. If not specified, the proportion refers to all key populations.

Scenario	Proportion of key population receiving HIV or syphilis testing per year			
	1 HIV test	2 HIV tests	1 syphilis test	2 syphilis tests
Baseline	50%	-	35% (FSW), 27% (MSM), 16% (PWID)	-
1. One HIV RDT	75%	-	35% (FSW), 27% (MSM), 16% (PWID)	-
2. One Dual HIV/syphilis RDT	75%		75%	-
3. One HIV RDT & One Dual HIV/syphilis RDT	75%	68%	75%	-
4. Two HIV RDTs	75%	68%	35% (FSW), 27% (MSM), 16% (PWID)	-
5. Two Dual HIV/syphilis RDT	75%	68%	75%	68%

* MSM=men who have sex with men, FSW=female sex workers, PWID=people who inject drugs, RDT=rapid diagnostic test.

We modeled increases in testing coverage by adjusting the percent of adults living with HIV (PLWH) on ART. The baseline scenario assumes 95% ART coverage among PLWH by 2028 (4.8% increase per year) based on recent ART scale-up in Viet Nam; test coverage increases by 6.0% per year with annual HIV testing (HIV RDT or dual RDT), and by 7.2% per year with biannual testing. Maximum test coverage is 95% for each model. All models assume ART coverage of 66% of men and 72% of women living with HIV in 2020 based on estimates from the Viet Nam HIV-AIDS Technical Working Group (TWG). We assume universal treatment among those who test positive for syphilis, individuals treated cannot become re-infected within the same year,[17] and no changes to syphilis prevalence under test case scenarios.

Cost-Effectiveness

Health impact was measured in DALYs averted, HIV infections averted, syphilis infections treated, and AIDS-related deaths averted over the 15-year time horizon. This time horizon was chosen because it reflects current HIV program planning in Viet Nam. Costs and health benefits were discounted at 3% annually per standard health economic evaluations. Incremental costs were calculated as costs incurred and averted by the testing strategy. We utilized WHO guidelines for cost-effectiveness threshold: less than gross domestic product (GDP) per capita is considered cost-effective in Viet Nam ($2,715 USD in 2019).[18]

Model calibration and sensitivity analyses

Models were calibrated to national HIV prevalence estimates for each key population. Monte Carlo sensitivity analyses were conducted to evaluate robustness of results to changes in: HIV and syphilis testing coverage, scenario program uptake rate, HIV and syphilis testing cost, HIV and syphilis treatment cost, average years on ART, and time horizon. **Table S1** shows the model parameters, ranges, and distributions used in the sensitivity analysis.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, conduct, reporting, or dissemination plans of our research.

Ethics approval

This study did not receive nor require ethics approval as it does not involve human or animal participants.

RESULTS

Increasing annual HIV test coverage from 50% (baseline) to 75% using an HIV RDT (scenario 1) or a dual RDT (scenario 2) is projected to avert 3,206 HIV infections and 660 AIDS-related deaths by 2035 in Viet Nam (**Table 3**). Annual testing using dual RDT led to treatment of an additional 7,719 syphilis cases over 15 years compared to using HIV RDT, but the number of HIV infections averted was the same. HIV testing with either HIV or dual RDT biannually (scenarios 3, 4, & 5) was projected to avert an additional 875 HIV infections and 183 AIDS-related deaths by 2035 compared to annual testing. Testing using a dual HIV/syphilis RDT biannually among key populations is projected to lead to an additional 124,460 syphilis cases treated by 2035, compared to annual testing using a dual RDT (116,680 total syphilis cases treated).

Table 3. Estimated HIV and syphilis infections, and cost-effectiveness of increased HIV and Dual HIV/syphilis testing among key populations in Viet Nam from 2020-2035. Each scenario refers to the number of tests per year. The baseline scenario assumes that 50% of key populations are tested for HIV each year and syphilis testing rates are specific to each sub-population (FSW, MSM, and PWID). Scenarios including one test per year assume a 75% test acceptance rate, and those that include two tests per year assume a 75% test acceptance rate for the first test, and a 68.5% test acceptance rate for the second test. *Incremental cases averted*, *Total DALYs averted,* and *ICERs* compare each scenario to the previous one.

		Scenario					
		Baseline	1 Dual Test	1 HIV Test	1 HIV & 1 Dual	2 HIV Tests	2 Dual Tests
HIV	New HIV infections	57,902	54,696	54,696	53,821	53,821	53,821
	AIDS deaths	13,877	13,217	13,217	13,034	13,034	13,034
	Total HIV DALYs	174,567,240	174,508,007	174,508,007	174,490,608	174,490,608	174,490,608
Syphilis	Total cases treated	108,901	116,680	108,901	116,680	108,901	233,361
	Total DALYs treated	3,466	3,713	3,466	3,713	3,466	7,426
Incremental cases averted	HIV infections averted	-	3,206	0	875	0	0
	HIV DALYs averted	-	59,233	0	17,399	0	0
	Syphilis cases treated	-	7,779	-7,779	7,779	-7,779	124,460
	Syphilis DALYs averted	-	248	-248	248	-248	7,426
Total DALYs averted (HIV & Syphilis)		-	-	59,481	-248	17,647	-248
Costs (USD)	Net Costs	$34,795,660	$30,123,774	$36,853,771	$47,943,060	$54,673,057	$57,292,031
	HIV testing	$16,491,955	-	$24,683,204	$19,677,541	$44,360,744	-
	HIV treatment averted	-	-$6,133,138	-$6,133,138	-$7,991,393	-$7,991,393	-$7,991,393
	Syphilis testing	$17,740,540	-	$17,740,540	-	$17,740,540	-
	Syphilis treatment	$563,165	$603,395	$563,165	$603,395	$563,165	$1,206,793
	Dual testing	-	$35,653,516	-	$35,653,516	-	$64,076,631
Total incremental costs		-	-$4,671,887	$6,729,997	$11,089,289	$6,729,997	$2,618,974
ICERs (cost per DALY averted)		-	**Cost-saving**	*Dom*	$1,024	*Dom*	$2,518

*DALY=disability adjusted life-years, USD=United States dollars, ICERs=incremental cost-effectiveness ratios, FSW=female sex workers, MSM=men who have sex with men, PWID=people who inject drugs

The most effective strategy was biannual testing with the dual RDT, which was projected to avert 4,081 HIV infections (7% of total infections), 76,632 HIV DALYs (0.04% of total HIV DALYs), and treat 124,460 cases of syphilis by 2035 compared to the baseline scenario. The discounted cost of implementing this scenario over 30 years is $57.3 million USD compared to $34.8 million USD for the baseline scenario. The testing cost of implementing biannual testing using the dual RDT is almost four times the cost of baseline testing with an HIV RDT ($64.1 million vs. $16.5 million, respectively), but an estimated $8.0 million USD in HIV treatment costs would be saved by biannual HIV testing, and $17.7 million USD in syphilis testing costs would be averted by using the dual RDT. The cost of biannual testing with an HIV RDT and continuing to test for syphilis with RPR is slightly higher than biannual testing with the dual RDT ($57.3 vs. $54.7 million USD, respectively), but the latter strategy treats an estimated 124,000 more cases of syphilis over 15 years.

Annual testing with the dual RDT is cost saving compared to the baseline scenario (**Figure 1**). Annual HIV testing with RDT is more expensive and averts fewer DALYs than with the dual RDT (strongly dominated). The next most efficient scenario is biannual testing using one dual RDT and one HIV RDT, which is cost-effective ($1,024 USD per DALY averted). Biannual testing with the dual RDT is also cost-effective ($2,518 USD per DALY averted) and more cost-effective than using the HIV RDT (weakly dominated). Despite slightly higher initial costs, the discounted cost of annual testing with a dual RDT becomes less than that of current testing within two years, due to decreased ART costs associated with HIV averted (**Figure S1**).

Sensitivity analyses including all scenarios found that an annual dual RDT (scenario 2) is cost-saving in 59% of the simulations and either cost-saving or cost-effective (at $2,715 per DALY averted) in all simulations (**Table S2**). In non-dominated scenarios (scenarios 2, 3, and 5), using dual RDT annually or biannually was cost-effective or cost-saving in most simulations, while biannual testing with one dual

RDT and one HIV RDT was cost-saving in only 31% of simulations (**Figure 2**). In univariate sensitivity analysis adjusting costs, our scenarios that involve one dual RDT (scenarios 2 and 3) remain cost-effective even after all costs (testing and treatment) are increased by 50%. In this sensitivity analysis, biannual dual testing is no longer cost-effective ($3,777 per DALY averted).

DISCUSSION

In our model, we found that implementing annual testing with the dual RDT at 75% coverage was cost-saving, averted more HIV infections, and treated more syphilis cases compared to annual testing using HIV RDT at 50% coverage and current syphilis testing in Viet Nam. While biannual testing with one dual RDT and one HIV RDT was projected to be more costly, it would avert more HIV and syphilis related DALYs and using dual RDT for both tests would avert additional DALYs attributed to syphilis. Increasing the frequency of HIV testing to one or two tests per year using only HIV RDTs, while continuing to test for syphilis using RPR, was not efficient compared to other strategies.

Implementing biannual testing substantially increases testing costs, but also prevents more HIV infections, therefore averting more ART-related costs. Increasing test frequency may be cost-saving or cost-effective although it incurs considerable costs in the near term while costs averted may not be observed for many years. Annual testing using a dual RDT can help offset some near-term costs as it is less expensive than using HIV RDT and syphilis RPR. Policymakers must weigh the health impact and cost-effectiveness of different testing scenarios over time against current affordability given HIV and syphilis testing budgets; however, using the dual RDT will help integrate syphilis testing within existing HIV testing programs, improving program efficiencies.[19]

Implementation of dual RDT is occurring in some settings; preliminary reports indicate that 48% of countries use dual RDT in ANC, and 25% use dual RDT in key populations, although the extent of this use is unknown (WHO HIV Testing Services, 2021). PEPFAR and the Global Fund cover dual RDT in ANC,[20] and there are multiple dual RDTs qualified by the Global Fund and WHO.[21] The use of dual RDT during ANC could be a model for improving HIV/STI integration among those at high risk for both HIV and syphilis, such as key populations, however, there are multiple operational challenges associated with using dual tests, namely that of integrating HIV and STI programs.[22]

Benefits of the dual test are its cost-effectiveness and potential to reach more at-risk individuals. Annual or biannual testing can enable earlier identification of HIV-positive individuals for faster ART initiation and prevention of onward transmission. Annual HIV testing for key populations is recommended by WHO, and more frequent testing (every 3-6 months) may be advised for those with individual risk factors, including those using pre-exposure prophylaxis (PrEP) and key populations presenting with STIs.[23] Individuals presenting with syphilis symptoms should also test for HIV, and using the dual RDT is less costly as compared to a syphilis RPR and HIV RDT. As policy makers scale up PrEP among key populations in Viet Nam, including at least one dual RDT in the testing algorithm may be more cost-effective than using HIV RDTs alone. In addition, using dual RDT tests can facilitate lay providers to offer both HIV and syphilis testing for their community.[24]

Our results were robust to sensitivity analyses, suggesting that testing annually or biannually using dual RDTs remains cost-effective if testing costs increase and HIV prevalence decreases. In scenarios involving dual RDT, the majority (>98%) of benefits, as measured in DALYs, come from averting HIV infections rather than treating syphilis due to the relatively larger burden of disease from HIV than syphilis. However, since the cost of a dual RDT is only slightly higher than the cost of an HIV RDT, it is cheaper to use a dual RDT than separate HIV RDT and syphilis RPR tests.

Increased HIV testing can reduce HIV-associated morbidity and mortality and transmission from PLHIV through early detection and initiation of ART. While models suggest high ART coverage would result in substantial declines in HIV incidence,[25, 26] empiric data from countries with population-level viral suppression exceeding 73% (e.g. Australia, eSwatini, and Thailand) have observed less significant reductions in HIV incidence relative to predictions from mathematical models.[27] Similarly, when high ART coverage was achieved in a series of cluster-randomized trials in sub-Saharan Africa, it resulted in decreased population-level HIV incidence; however, this decrease was insufficient to end HIV as a public health threat.[28–31] These discrepancies may be attributed to delayed diagnosis and ART initiation following infection,[32, 33] and gaps in the 95-95-95 targets for some population groups, for example young men and key populations. More frequent HIV testing strategies could increase earlier diagnosis and initiation on ART, and focusing testing and linkage efforts on key populations could reduce the access and coverage disparities in these groups. However, more frequent testing will also increase program costs, not only through additional commodity procurement, but also for health systems, program coordination, and outreach. In settings of concentrated HIV epidemics, health planners may benefit from targeting limited testing resources towards high-risk groups such as key populations.

Dual RDTs may also increase syphilis testing frequency and coverage among key populations who are more likely to access HIV testing. Previous research has shown that coupling rapid syphilis testing in ANC may also increase HIV test coverage in LMICs, particularly in settings where HIV test coverage is low.[34] This strategy may be similarly effective at increasing test coverage for both diseases among key populations, as well as augment current ANC testing by reaching women in key populations who present late or are missed by ANC services. While there is a lack of data on dual RDTs among key populations, models of dual RDT during ANC have been shown to be cost-saving or cost-effective among both key populations and the general population of pregnant women.[7, 35] While dual RDTs are likely more effective in the context of ANC since testing can avert more adverse outcomes associated with congenital syphilis and mother-to-child HIV transmission, we find dual RDTs may also be cost-effective among non-pregnant key populations.

Our results are consistent with previously published models that show expanded testing and early access to ART for key populations in Viet Nam will cost-effectively reduce the country's HIV burden.[36, 37] Additionally, models from both low- and high-resource countries suggest HIV testing every 3-6 months among key populations can be cost-effective in concentrated epidemics.[38][39] However, HIV risk within key populations is not homogenous; further targeting of higher-risk groups within key populations may be needed to achieve efficient testing regimens. While we examine the impact of increased testing frequency among key populations as a whole, previous research has described the benefits of targeting high-risk groups within key populations.[40] Individuals who engage in risky behaviors, such as those with more sexual partners, practicing unprotected sex, or needle sharing may benefit from additional testing or linkage to HIV prevention such as PrEP. Further research is needed on the optimal testing intervals for higher-risk groups of key populations.

Approximately one-third of key populations are not aware of their HIV status. Programs focusing on HIV testing and treatment among FSW and PWID in Viet Nam have shown success in reducing HIV prevalence; however, less than a third of MSM reported testing for HIV in 2015, likely contributing to increases in HIV prevalence among MSM in the past decade.[41] Annual syphilis testing among key populations in Viet Nam is similarly low, ranging from 16% among PWID to 36% among FSW. [14–16] Due to high dual prevalence of HIV and syphilis among key populations, dual testing is a promising strategy to increase testing coverage and linkage to care.

Our analysis has several limitations. We did not include the cost of scaling-up and training providers in administering dual RDTs. However, RDT are easy to use and can be administered by a lay provider, and rapid results can minimize loss to follow-up. Overall, dual RDTs have been shown to have adequate performance in field settings in Viet Nam among key populations.[42] Dual RDTs may also increase HIV test coverage as they can be easily conducted by community health workers outside of healthcare settings, and they may be more acceptable to some members of key populations who are concerned about stigma associated with testing.[43] Despite this, some additional training, supervision, and support will be needed to scale-up dual RDT use among key populations.

Some model assumptions regarding the timing of HIV and syphilis testing may be inaccurate. We assumed in scenarios that included a dual RDT, additional syphilis RPR tests would not be conducted. PLWH who know their status and present for syphilis screening do not need an HIV test. We assume regular testing intervals for the entire population in each scenario, but it is possible people who engage in risky behaviors or experience symptoms may seek more frequent retesting than biannually. We did not include the increased costs of outreach to achieve increased test coverage of key populations. Considerable expansions of first time testing among MSM in Viet Nam have recently been achieved through social media campaigns, perhaps providing a guide for cost-effectively increasing testing uptake among key populations.[41, 44] We also did not consider the burden that increasing the testing coverage and frequency may have on the health system; however, as testing may be conducted effectively using lay providers, increased testing may not substantially impact the provision of other services.[43] Although targeting key populations in lower prevalence regions may be more difficult and costly, these results are robust to increased costs and it will likely remain an effective use of resources. We assume that syphilis screening will not impact syphilis prevalence rates. Increased screening may reduce prevalence by increasing early treatment, but syphilis screening also has the potential to increase prevalence as individuals with latent syphilis are unlikely to transmit the infection to others unless they are treated and then infected again. Finally, there is limited data on population size, HIV and syphilis prevalence, and health seeking behaviors among key populations. We based our model input on estimates included in published literature as well as Viet Nam country sources.

Since data on the impact of retesting on population HIV incidence is limited, we made conservative assumptions about the frequency of linkage to care and ART use following retesting. We assumed that HIV testing frequency would increase in Viet Nam among key populations in the baseline scenario but testing frequency would increase more quickly under the other scenarios. Because of this, we believe our estimates of the impact of increased testing frequency are conservative.

Our study suggests that annual or biannual HIV and syphilis testing among key populations in Viet Nam using a dual RDT will increase HIV and syphilis detection and treatment, while remaining cost-saving or cost-effective. Integrating HIV and other STI testing can streamline services as well as expand testing and help countries with epidemics concentrated in key populations reach 95-95-95 targets.

COMPETING INTERESTS

The authors declare no competing interests.

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CONTRIBUTORSHIP STATEMENT

CJ and AD devised the project and the main conceptual ideas. DC, DG, and RB parameterized the model. DC and DG carried out the model implementation. VH and SVH provided model feedback. All authors provided critical feedback and helped shape the research, analysis, and manuscript.

DATA SHARING STATEMENT

Extra data is available by emailing David Coomes, dcoomes@uw.edu

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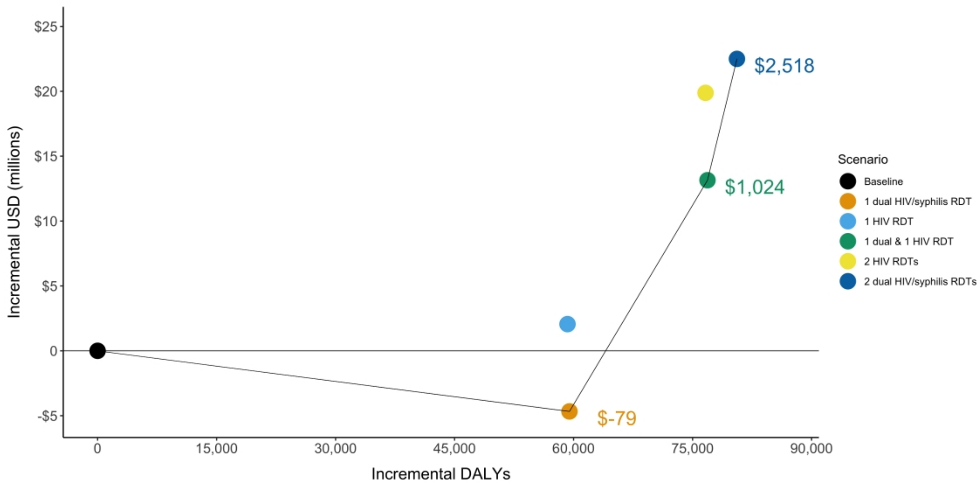
FIGURE LEGENDS

Figure 1. Efficiency frontier presenting the total disability adjusted life years (DALYs) and costs for five testing scenarios among key populations. The solid line indicates the scenarios that are not dominated by other scenarios. Dominated indicates that a scenario is either more costly and less effective or has a higher ICER than a scenario that is more effective. The ICERs for the non-dominated scenarios are shown. DALYs=disability adjusted life-years, ICER=incremental cost-effectiveness ratio, RDT=rapid diagnostic test, USD=United States dollars

Figure 2. Sensitivity analysis of non-dominated scenarios using a Monte Carlo simulation of the cost effectiveness of HIV/syphilis dual testing among key populations in Viet Nam. Plot shows 10,000 iterations in which 17 key parameters were randomly adjusted. All points below the green line are cost-effective at $2,715 per DALY averted and those below the solid black line (y-intercept) are cost-saving. Only non-dominated scenarios are shown in this figure; cost-effectiveness of *1 Dual Test* is compared to baseline, *1 HIV Test & 1 Dual Test* is compared to *1 Dual Test*, and *2 Dual Tests* is compared to *1 HIV Test & 1 Dual Test*. DALYs=disability adjusted life-years, ICER=incremental cost-effectiveness ratio, RDT=rapid diagnostic test, USD=United States dollars.



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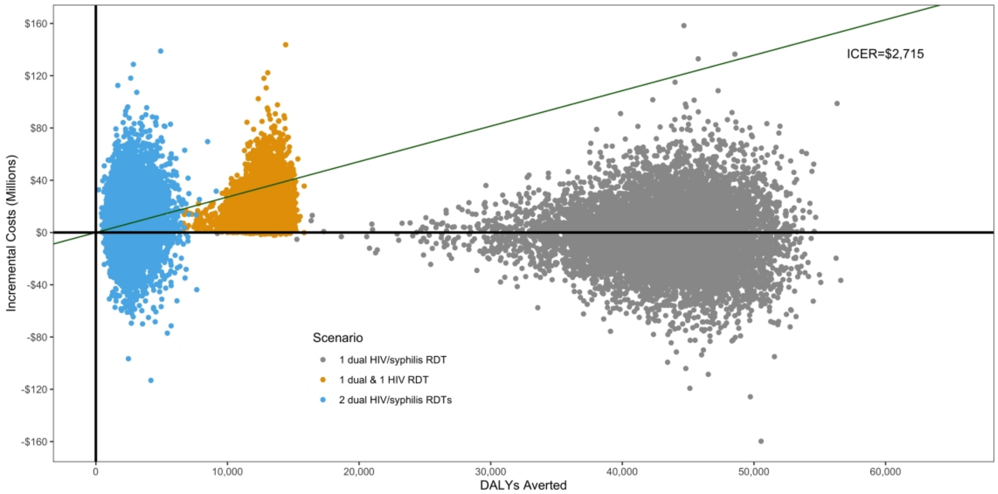

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Table S1. Parameters and probability distributions for Monte Carlo simulation. Table shows the baseline model parameter values and the probability distributions used for random draws of 17 variables for 10,000 Monte Carlo simulations. Beta distributions were used for all proportion parameters. For the beta distribution, the alpha and beta parameters were calculated as the baseline value multiplied by 100, except for the *impact* parameter where an alpha and beta of 25 was used. Gamma distributions were used for all other parameters. For the gamma distribution, the alpha parameter was calculated as the square of the baseline parameter divided by the square of the standard deviation. The beta parameter was calculated as the square of the standard deviation divided by the baseline parameter.

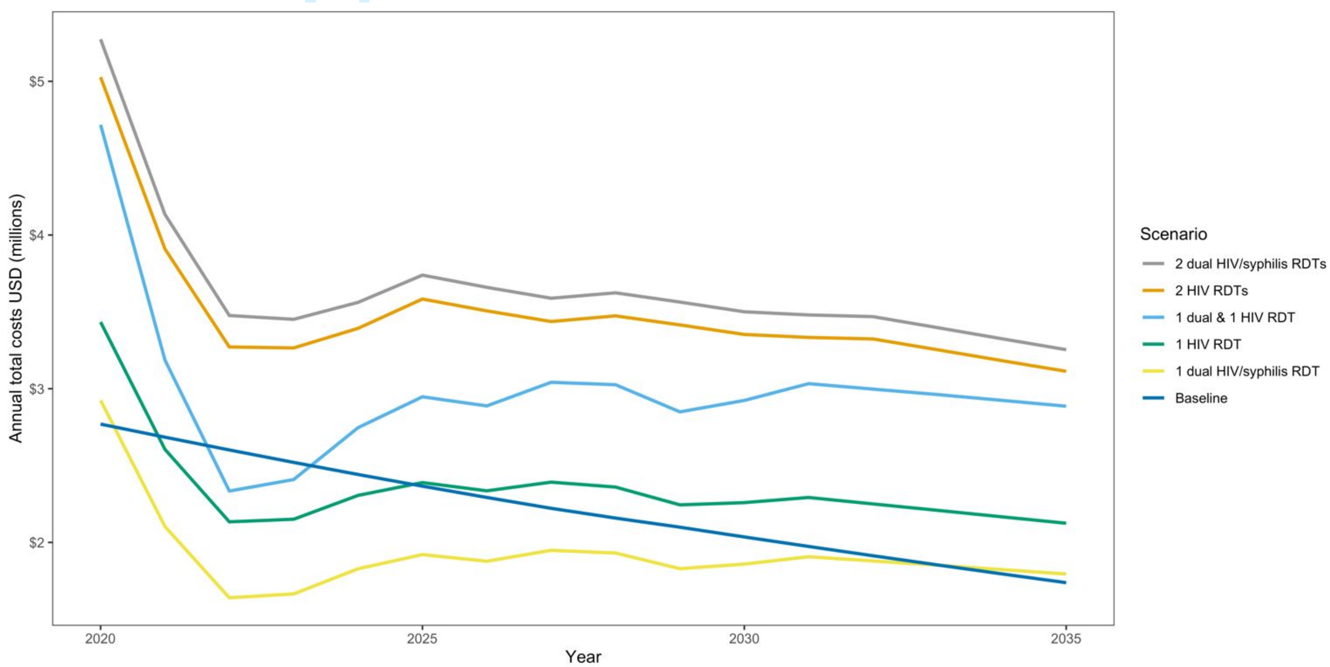
Model Parameter	Baseline value	Distribution	St. Dev	alpha/beta
Baseline HIV test acceptance	50%	Beta	N/A	50
Recommended test acceptance	75%	Beta	N/A	75
Additional test drop off rate	10%	Beta	N/A	10
HIV Lay Test Cost	$4.50	Gamma	$3.00	N/A
Syphilis RPR1 Cost	$6.28	Gamma	$3.50	N/A
HIV/Syphilis Dual Test Cost	$6.50	Gamma	$3.50	N/A
ART Treatment Cost	$285	Gamma	$50	N/A
Syphilis Treatment Cost	$6.50	Gamma	$3.50	N/A
Avg Years on ART	25	Gamma	3	N/A
Time Horizon	2035	Gamma	3	N/A
Impact	100%	Beta	N/A	25
Baseline Syphilis test acceptance FSW	35%	Beta	N/A	35
Baseline syphilis test acceptance MSM	27%	Beta	N/A	27
Baseline syphilis test acceptance PWID	16%	Beta	N/A	16
Baseline syphilis prevalence FSW	2.1%	Beta	N/A	2.1
Baseline syphilis prevalence MSM	6.7%	Beta	N/A	6.7
Baseline syphilis prevalence PWID	0.3%	Beta	N/A	0.3

Table S2. Sensitivity analysis of all scenarios using a Monte Carlo simulation. Table shows the percentage of simulations (10,000 iterations) in which each scenario is cost-effective (at $500 or $2,715 per DALY averted), cost-saving, or less-effective. Less effective scenarios are both less effective and more costly as compared to the scenario above. Scenarios are arranged in order of increasing cost and each scenario is compared to the one immediately above; 1 Dual HIV/syphilis RDT is compared to the baseline scenario.

Scenario	**Cost-effective ($500)**	**Cost-effective ($2,715)**	**Cost-saving**	**Less effective**
1 Dual HIV/syphilis RDT	87%	100%	59%	0%
1 HIV RDT	11%	12%	11%	69%
1 Dual HIV/syphilis RDT & 1 HIV RDT	45%	87%	31%	0%
2 HIV RDTs	11%	12%	11%	69%
2 Dual HIV/syphilis RDTs	49%	55%	48%	0%

DALY=disability adjusted life-year, RDT=rapid diagnostic test

Figure S1. Cost pressure analysis of testing scenarios. Figure shows the discounted cost over time of each scenario. Costs are discounted 3% with a time horizon from 2020 – 2035. Baseline costs include testing costs assuming that 50% of key populations are tested for HIV each year and syphilis testing rates are specific to each sub-population (FSW, MSM, and PWID), and syphilis treatment costs. All other scenarios include the cost of HIV treatment averted compared to the baseline scenario, testing costs, and syphilis treatment costs. Scenarios including one test per year assume a 75% test acceptance rate, and those that include two tests per year assume a 75% test acceptance rate for the first test, and a 68.5% test acceptance rate for the second test. Each scenario refers to the number of tests per year. RDT=rapid diagnostic test, USD=United States dollars



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Cost-effectiveness of implementing HIV and HIV/syphilis dual testing among key populations in Viet Nam: a modeling analysis

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Cost-effectiveness of implementing HIV and HIV/syphilis dual testing among key populations in Viet Nam: a modeling analysis

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ABSTRACT

Objectives

Key populations, including sex workers, men who have sex with men, and people who inject drugs, have a high risk of HIV and sexually transmitted infections (STIs). We assessed the health and economic impacts of different HIV and syphilis testing strategies among three key populations in Viet Nam using a dual HIV/syphilis rapid diagnostic test (RDT).

Setting

We used the Spectrum AIDS Impact Model to simulate the HIV epidemic in Viet Nam and evaluated five testing scenarios among key populations. We used a 15-year time horizon and a provider perspective for costs.

Participants

We simulate the entire population of Viet Nam in the model.

Interventions

We modeled five testing scenarios among key populations: 1) annual testing with an HIV rapid diagnostic test (RDT), 2) annual testing with a dual RDT, 3) biannual testing using dual RDT and HIV RDT, 4) biannual testing using HIV RDT, and 5) biannual testing using dual RDT.

Primary and secondary outcome measures

The primary outcome is incremental cost-effectiveness ratios (ICERS). Secondary outcomes include HIV and syphilis cases.

Results

Annual testing using a dual HIV/syphilis RDT was cost-effective ($10 per disability-adjusted life year (DALY)) and averted 3,206 HIV cases and treated 27,727 syphilis cases compared to baseline over 15 years. Biannual testing using one dual test and one HIV RDT ($1,166 per DALY), or two dual tests ($5,672 per DALY) both averted an additional 875 HIV cases, although only the former scenario was cost-effective. Annual or biannual HIV testing using HIV RDTs and separate syphilis tests were more costly and less effective than using one or two dual RDTs.

Conclusions

Annual HIV and syphilis testing using dual RDT among key populations is cost-effective in Vietnam and similar settings to reach global reduction goals for HIV and syphilis.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Strength: Our model parameters are informed by empiric data including demographic, behavioral, and biological data from government sources, surveys, surveillance, publicly available reports, databases, and peer-reviewed literature.
- Strength: We assess the impact of five testing scale up scenarios using both HIV RDT and dual HIV/syphilis RDT and conduct sensitivity analyses to evaluate uncertainty in model results.
- Limitation: Due to limited data, we make assumptions regarding the timing and uptake of HIV and syphilis testing among key populations that may be inaccurate.
- Limitation: Our model conservatively assumes that increased syphilis testing and treatment will not impact syphilis prevalence, which is currently unknown.

INTRODUCTION

Key populations, including people who inject drugs (PWID), men who have sex with men (MSM), sex workers (SW), and transgender populations are at higher risk of acquiring both HIV and syphilis. HIV incidence is significantly higher among key populations compared to the general population in all geographic regions; however, differences vary substantially by region and by key population.[1] While key populations and their sexual partners represent approximately 25% of new HIV cases in sub-Saharan Africa, they represent 80% of new HIV cases in the rest of the world.[2] Recent data suggests syphilis incidence, while generally remaining stable in low- and middle-income countries (LMIC), is increasing among key populations, particularly MSM.[1, 3, 4] World Health Organization (WHO) HIV testing guidelines recommend HIV retesting at least annually for key populations and more frequent testing (3-6 months) for those with high ongoing risk.[5] WHO guidelines for syphilis screening depend on population and setting. Laboratory-based syphilis testing remains common, however rapid diagnostic tests (RDTs) for syphilis are increasingly available and may be used to improve access to testing and treatment, including among key populations who are disproportionately affected by both HIV and syphilis.[6] With the introduction of prequalified dual HIV/syphilis RDTs, and the recent WHO recommendation to offer dual HIV/syphilis testing in antenatal care (ANC) settings,[7] it is important to evaluate how further integration and expansion of dual HIV/syphilis testing could benefit key populations.

Since 2015, WHO has recommended immediate initiation of antiretroviral therapy (ART) for all people living with HIV (PLHIV) [8] and the United Nations 95-95-95 targets aim to diagnose 95% of PLHIV, provide 95% of PLHIV who know their status with ART, and ensure 95% PLHIV on ART are virally suppressed.[9] Despite progress towards these goals – in 2019 81% of PLHIV knew their HIV status and 67% were on ART – this progress is uneven; only 2/3 of key populations are aware of their HIV status.[2] While key populations lag behind the general population in all phases of testing, linkage to treatment, and viral suppression, the largest gap exists in testing.[10] WHO has also developed a global strategy on sexually transmitted infections (STIs) which aims for a 90% reduction in syphilis incidence by 2030, and 70% of key populations to have access to STI and HIV services, including prevention, testing, and treatment.[11] Increased syphilis testing and treatment may reduce syphilis burden among key and general populations, as well as HIV incidence since early symptomatic syphilis increases risks of HIV acquisition and transmission.[3] Currently, WHO recommends syphilis testing for pregnant women and key populations, however, the optimal frequency of syphilis testing is unknown and recommendations on syphilis testing for other populations are not available.

In Viet Nam, the national HIV prevalence is <1% in the general population, and significantly higher in key populations, with prevalence ranging between 3-13% among PWID, MSM, and female sex workers (FSW). Similarly, syphilis prevalence among MSM (6.7%) and FSW (2.1%) are also higher than that of the general population (0.3%).[12] With budgetary constraints in HIV/STI programs and the health sector, identifying cost-effective strategies for targeted HIV and syphilis testing among key groups in Viet Nam is crucial to inform policymakers seeking to optimize resource allocation to maximize population health. We modeled the health impacts and costs associated with varying frequencies of HIV and syphilis testing for key populations, using test scenarios that include a dual HIV/syphilis RDT.

METHODS

Model

We used the AIDS Impact Model within the Spectrum software package (v 5.76) to simulate the HIV epidemic in Viet Nam from 2020-2035. The model estimates annual HIV incidence, AIDS mortality, and disability. We simulated the impact of increasing HIV testing frequency among key populations using the Goals model within Spectrum, as previously described.[13] Briefly, Spectrum is a deterministic, compartmental mathematical model of HIV transmission stratified by sex and age. Transmission is simulated through male-female and male-male sex acts, needle sharing for injection, and maternal-to-child transmission with specific transmission probabilities for each route. One can further specify parameters for low- and medium-risk groups, as well as high-risk categories including FSW, MSM, and PWID.[1] Each of these high-risk categories is nested within their parent categories and

[1] Low-risk heterosexuals are those in stable couples while medium-risk heterosexuals are those that engage in casual sex but are not in a high-risk group (high risk groups: MSM, FSW, PWID).

interact with one another. For example, among MSM, a proportion is assumed to also have female sexual partners. These high-risk categories can be parameterized to have differential rates of partnership and uptake of interventions. The model was parameterized with demographic, behavioral, and biological data from government sources, surveys, surveillance, publicly available reports, databases, and peer-reviewed literature.

To estimate syphilis burden, we used key population size estimates from the Goals model and population-specific estimates of prevalence;[12] we estimate the number of persons in key populations testing positive and treated for syphilis infection under each scenario. This model assumes that syphilis testing and treatment does not impact syphilis prevalence, although increased screening could potentially result in reduced, unchanged, or increased syphilis prevalence depending on coverage.[14, 15] For both HIV and syphilis, disability-adjusted life years (DALYs) are calculated for each scenario. Model key parameters are shown in **Table 1**.

Settings and Populations

We modeled three key populations: MSM, PWID, and FSW (and their clients) within the HIV epidemic in Viet Nam, using national level HIV prevalence and syphilis prevalence estimates for each key population **(Table 1)**.

Table 1. Model parameters for Spectrum input and cost-effectiveness analysis of HIV and syphilis testing scale up among key populations in Viet Nam. [a] = 2018 Viet Nam HIV Sentinel Surveillance. [b] = 2019 Viet Nam HIV Sentinel Surveillance. * = Spectrum model prior. ** = assumed. *** = Based on information from in-country source.

Model parameter	Value
HIV Prevalence	
MSM (incl. TGW)[a]	10.8%
PWID[b]	12.7%
FSW[a]	3.6%
Syphilis Prevalence[12]	
MSM (incl. TGW)	6.7%
PWID	0.3%
FSW	2.1%
Baseline syphilis test acceptance	
MSM (incl. TGW)[16],[17],[18]	27%
PWID[19]	16%
FSW[20],[21]	35%
Syphilis DALYs averted[22]	
DALYs averted per syphilis case treated	0.04
ART	

2019 Coverage***	70%
Annual Scale-Up**	4.8%
Transmission Reduction Efficacy*	70%
Mortality Reduction Efficacy*	80%
Other Prevention	
Condom Use**	50%
Condom Efficacy*	80%
PrEP Coverage (MSM incl. TGW)**	5%
PrEP Efficacy*	90%
PrEP Adherence*	80%
Costs* **	
HIV Lay Test†	$4.50
Syphilis RPR†	$6.28
Syphilis TPHA†	$10.26
HIV/Syphilis Dual Test†	$6.50
ART‡	$285
Syphilis Treatment	$6.50
Time Horizon	2020 - 2035
Discount Rate	3%

† Testing costs include labor, incentives, travel costs, and test kits. Primary cost driver between tests is the cost of the test kit.
‡ ART cost includes labor, laboratory monitoring costs, ARVs, and other recurring costs.
* MSM=men who have sex with men, FSW=female sex workers, PWID=people who inject drugs, TGW=transgender women, ART=antiretroviral therapy, PrEP=pre-exposure prophylaxis, syphilis RPR=syphilis rapid plasma reagin, syphilis TPHA=treponema pallidum hemagglutination assay, DALY=disability-adjusted life year

Scenarios

Our baseline scenario estimates annual HIV testing based on current WHO recommendations and estimated HIV testing rates among key populations,[5] and syphilis testing based on observed uptake. In the baseline scenario, we assume 50% of individuals in key populations test annually for HIV, and syphilis screening with a non-treponemal test (RPR) occurs at rates specific to each key population (**Table 2**).[18–20] Individuals who test positive using RPR are given a confirmatory treponemal (TPHA) test. We modeled HIV RDTs as WHO recommend, limiting the use of lab-based testing such as western blot, especially in hard-to-reach populations, to increase access and limit the loss to follow up.[23] We considered alternative scenarios with varying testing frequency and test type (separate HIV and syphilis RPR, or a combined dual syphilis/HIV RDT) among key populations from 2020 to 2035. Scenarios modeled include: **1)** annual HIV testing with RDT and baseline syphilis RPR testing, **2)** annual testing with dual RDT, **3)** biannual testing (2 times per year), first with dual RDT and then with HIV RDT, **4)** biannual HIV testing with RDT and baseline syphilis RPR testing, and **5)** biannual testing with dual RDT **(Table 2)**. We assumed 75% test acceptance for the first test in all scenarios except baseline, and 90% of those who accepted the first test would accept the second test in all scenarios that include biannual testing. All individuals who test positive for syphilis using the dual test are then tested using RPR and TPHA per current Viet Nam country guidelines.

Table 2: HIV/syphilis testing scenarios among key populations in Viet Nam. The table cells show the proportion of key populations in Viet Nam that receive each test per year. If not specified, the proportion refers to all key populations.

Scenario	Proportion of key population receiving HIV or syphilis testing per year			
	1 HIV test	2 HIV tests	1 syphilis test	2 syphilis tests
Baseline	50%	-	35% (FSW), 27% (MSM), 16% (PWID)	-
1. One HIV RDT	75%	-	35% (FSW), 27% (MSM), 16% (PWID)	-
2. One Dual HIV/syphilis RDT	75%		75%	-
3. One HIV RDT & One Dual HIV/syphilis RDT	75%	68%	75%	-
4. Two HIV RDTs	75%	68%	35% (FSW), 27% (MSM), 16% (PWID)	-
5. Two Dual HIV/syphilis RDT	75%	68%	75%	68%

* MSM=men who have sex with men, FSW=female sex workers, PWID=people who inject drugs, RDT=rapid diagnostic test.

We modeled increases in testing coverage by adjusting the percent of people living with HIV (PLWH) on ART; in scenarios with increased testing there is a higher probability that an individual in the model will initiate ART throughout the year. The baseline scenario assumes 95% ART coverage among PLWH by 2028 (4.8% increase per year) based on recent ART scale-up in Viet Nam; test coverage increases by 6.0% per year with annual HIV testing (HIV RDT or dual RDT), and by 7.2% per year with biannual testing. Maximum test coverage is 95% for each model. All models assume ART coverage of 66% of men and 72% of women living with HIV in 2020 based on estimates from the Viet Nam HIV-AIDS Technical Working Group (TWG). Modeled HIV incidence per year is shown in **Figure S1**. We assume universal treatment among those who test positive for syphilis, individuals treated cannot become re-infected within the same year,[24] and no changes to syphilis prevalence under test case scenarios.

Costs

Testing cost inputs include cost per HIV RDT test, rapid plasma reagin (RPR), treponema pallidum hemagglutination (TPHA), and dual HIV/syphilis RDT. We used local data on the personnel, commodities, and transport costs associated with lay testing and estimate costs (**Table 1**). ART costs include personnel, commodities, clinical follow-up, and laboratory monitoring. This analysis includes the costs of intervention delivery and treatment (Benzathine penicillin G and ART) but does not consider additional averted sequelae costs such as the treatment of opportunistic infections due to uncontrolled HIV. All costs are from the provider's perspective and reported in 2019 US dollars.

Cost-Effectiveness

Health impact was measured in DALYs averted, HIV infections averted, syphilis infections treated, and AIDS-related deaths averted over the 15-year time horizon. This time horizon was chosen because it reflects current HIV program planning in Viet Nam. HIV outcomes are modeled for the entire population of Viet Nam while syphilis outcomes are specific to key populations. Costs and health benefits were discounted at 3% annually per standard health economic evaluations.[25] Incremental costs were calculated as costs incurred and averted by the testing strategy. We utilized WHO guidelines for cost-effectiveness threshold: less than gross domestic product (GDP) per capita is considered cost-effective in Viet Nam ($2,715 USD in 2019).[26]

Model calibration and sensitivity analyses

Models were calibrated to national HIV prevalence data for each key population. Monte Carlo sensitivity analyses were conducted to evaluate robustness of results to changes in: HIV and syphilis testing coverage, scenario program uptake rate, HIV and syphilis testing cost, HIV and syphilis treatment cost, average years on ART, and time horizon. **Table S1** shows the model parameters, ranges, and distributions used in the sensitivity analysis.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, conduct, reporting, or dissemination plans of our research.

RESULTS

Increasing annual HIV test coverage from 50% (baseline) to 75% using an HIV RDT (scenario 1) or a dual RDT (scenario 2) is projected to avert 3,206 HIV infections and 660 AIDS-related deaths by 2035 in Viet Nam (**Table 3**). Annual testing using dual RDT led to treatment of an additional 27,727 syphilis cases over 15 years compared to using HIV RDT, but the number of HIV infections averted was the same. HIV testing with either HIV or dual RDT biannually (scenarios 3, 4, & 5) was projected to avert an additional 875 HIV infections and 183 AIDS-related deaths by 2035 compared to annual testing. Testing using a dual HIV/syphilis RDT biannually among key populations is projected to lead to an additional 88,401 syphilis cases treated by 2035, compared to annual testing using a dual RDT (88,953 total syphilis cases treated).

Table 3. Estimated HIV and syphilis infections, and cost-effectiveness of increased HIV and Dual HIV/syphilis testing among key populations in Viet Nam from 2020-2035. Each scenario refers to the number of tests per year. The baseline scenario assumes that 50% of key populations are tested for HIV each year and syphilis testing rates are specific to each sub-population (FSW, MSM, and PWID). Scenarios including one test per year assume a 75% test acceptance rate, and those that include two tests per year assume a 75% test acceptance rate for the first test, and a 68.5% test acceptance rate for the second test. *Incremental cases averted*, *Total DALYs averted,* and *ICERs* compare each scenario to the previous one.

		Scenario					
		Baseline	1 Dual Test	1 HIV Test	1 HIV & 1 Dual	2 HIV Tests	2 Dual Tests
HIV	New HIV infections	57,902	54,696	54,696	53,821	53,821	53,821
	AIDS deaths	13,877	13,217	13,217	13,034	13,034	13,034
	Total HIV DALYs	174,567,240	174,508,007	174,508,007	174,490,608	174,490,608	174,490,608
Syphilis	Total cases treated	88,953	116,680	88,953	116,680	88,953	177,354
	Total DALYs treated	2,831	3,713	2,831	3,713	2,831	5,644
Incremental cases averted	HIV infections averted	-	3,206	0	875	0	0
	HIV DALYs averted	-	59,233	0	17,399	0	0
	Syphilis cases treated	-	27,727	-27,727	27,727	-27,727	88,401
	Syphilis DALYs averted	-	882	-882	882	-882	2,813
Total DALYs averted (HIV & Syphilis)		-	60,115	-882	18,281	-882	2,813
Costs (USD)	Net Costs	$31,036,672	$31,659,182	$33,094,783	$51,942,954	$53,378,555	$62,896,039
	HIV testing	$16,491,955	-	$24,683,204	$22,142,027	$46,825,230	-
	HIV treatment averted	-	-$6,133,138	-$6,133,138	-$7,991,393	-$7,991,393	-$7,991,393
	Syphilis testing	$14,084,698	$1,535,409	$14,084,698	$1,535,409	$14,084,698	$2,333,826
	Syphilis treatment	$460,019	$603,395	$460,019	$603,395	$460,019	$917,162
	Dual testing	-	$35,653,516	-	$35,653,516	-	$67,636,444
Total incremental costs		-	$622,510	$1,435,601	$18,848,171	$1,435,601	$9,517,484
ICERs (cost per DALY averted)		-	$10	*Dom*	$1,166	*Dom*	$5,672

*DALY=disability adjusted life-years, USD=United States dollars, ICERs=incremental cost-effectiveness ratios, FSW=female sex workers, MSM=men who have sex with men, PWID=people who inject drugs

The most effective strategy was biannual testing among MSM, PWID, and FSW with the dual RDT, which was projected to avert 4,081 HIV infections (7% of total infections), 76,632 HIV DALYs (0.04% of total HIV DALYs), and treat 88,401 cases of syphilis by 2035 compared to the baseline scenario. The discounted cost of implementing this scenario over 30 years is $62.9 million USD compared to $31.0 million USD for the baseline scenario. The testing cost of implementing biannual testing using the dual RDT is approximately four times the cost of baseline testing with an HIV RDT ($67.6 million vs. $16.5 million, respectively), but an estimated $8.0 million USD in HIV treatment costs would be averted by biannual HIV testing, and $11.8 million USD in syphilis testing costs would be averted by using the dual RDT. The cost of biannual testing with an HIV RDT and continuing to test for syphilis with RPR is higher than biannual testing with one dual RDT and one HIV RDT ($53.4 vs. $51.9 million USD, respectively), but using one dual test in biannual testing treats an estimated 28,000 more cases of syphilis over 15 years while averting the same number of HIV cases.

Annual testing with the dual RDT is cost-effective compared to the baseline scenario ($10 USD per DALY averted) (**Figure 1**). Annual HIV testing with HIV RDT is more expensive and averts fewer DALYs than with the dual RDT (strongly dominated). The next most efficient scenario is biannual testing using one dual RDT and one HIV RDT, which is cost-effective ($1,166 USD per DALY averted). Biannual testing with HIV RDT is less effective and more costly than biannual testing using one dual RDT and one HIV RDT, while biannual testing using the dual RDT provides additional health benefits but is not cost-effective ($5,672 USD per DALY averted). Despite slightly higher initial costs, the discounted cost of annual testing with a dual RDT becomes less than that of current testing within two years, due to decreased ART costs associated with HIV averted (**Figure S2**).

Sensitivity analyses including all scenarios found that an annual dual RDT (scenario 2) is cost-saving in 52% of the simulations and either cost-saving or cost-effective (at $2,715 per DALY averted) in all simulations (**Table S2**). Biannual testing using one dual RDT and one HIV RDT was cost-effective in 86% of simulations, but cost-saving in only 1% of simulations (**Figure 2**). Biannual testing using two dual RDTs was cost-effective in 45% of simulations and cost-saving in 31% of simulations as compared to biannual testing with one dual RDT and one HIV RDT. In univariate sensitivity analysis adjusting costs, our scenarios that involve one dual RDT (scenarios 2 and 3) remain cost-effective even after all costs (testing and treatment) are increased by 50% ($16 and $1,705 USD per DALY averted respectively).

DISCUSSION

In this modeling analysis we found that implementing annual testing among key populations with the dual RDT at 75% coverage was cost-effective, averted more HIV infections, and treated more syphilis cases compared to annual testing using HIV RDT at 50% coverage and current syphilis testing in Viet Nam. While biannual testing with one dual RDT and one HIV RDT was projected to be more costly, it would avert more HIV and syphilis related DALYs, and using dual RDT for both tests would avert additional DALYs attributed to syphilis, although this latter scenario was not found to be cost-effective. Increasing the frequency of HIV testing to one or two tests per year using only HIV RDTs (scenario 1 & 4), while continuing to screen for syphilis using RPR, was not efficient compared to other strategies.

Implementing biannual testing substantially increases testing costs, but also prevents more HIV infections, therefore averting more HIV healthcare costs, including ART and hospitalizations. Increasing test frequency may be cost-saving or cost-effective, although it incurs considerable costs in the near term while costs averted may not be observed for many years. Annual testing using a dual RDT can help offset some near-term costs as it is less expensive than using HIV RDT and syphilis RPR. Policymakers must weigh the health impact and cost-effectiveness of different testing scenarios over time against current affordability; however, using the dual RDT will help integrate syphilis testing within existing HIV testing programs, improving program efficiencies.[27]

Implementation of dual RDT is occurring in some settings; preliminary reports indicate that 49 countries have adopted policies to use dual HIV/syphilis RDT in ANC, and 15% of reporting counties have policies to support their use in key populations, although the extent of implementation is unknown.[28] The President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund both fund dual RDT in ANC,[29] and there are multiple dual RDTs prequalified by the WHO.[30] The use of dual RDT during ANC could be a model for improving HIV/STI integration, particularly among those at high risk for both HIV and syphilis, such as key populations, however, there are operational challenges associated with integrating HIV and STI programs and delivering person-centered diagnosis, treatment, and prevention services.[31]

Benefits of the dual test are its potential to cost-effectively reach more at-risk individuals at the point-of-care. Annual or biannual testing can enable earlier identification of HIV-positive individuals for faster ART initiation and prevention of onward transmission. Annual HIV testing for key populations is recommended by WHO, and more frequent testing (every 3-6 months) may be advised for those with individual risk factors, including those using pre-exposure prophylaxis (PrEP) and key populations presenting with STIs.[23] Individuals presenting with syphilis symptoms should also test for HIV, and using the dual RDT is less costly as compared to a syphilis RPR and HIV RDT. As policymakers scale up PrEP among key populations in Viet Nam, including at least one dual RDT in the testing algorithm may be more cost-effective than using HIV RDTs alone. In addition, using dual RDT tests can facilitate lay providers to offer both HIV and syphilis testing for their community.[32]

Our results were robust to sensitivity analyses, suggesting that testing annually or biannually using dual RDTs remains cost-effective if testing costs increase and HIV prevalence decreases. In scenarios involving dual RDT, the majority (>98%) of benefits, as measured in DALYs, come from averting HIV infections rather than treating syphilis due to the relatively large burden of disease from HIV compared to syphilis. However, since the cost of a dual RDT is only slightly higher than the cost of an HIV RDT, it is cheaper to use a dual RDT than separate HIV RDT and syphilis RPR tests in situations where both tests are recommended.

Increased HIV testing can reduce HIV-associated morbidity and mortality and transmission from PLHIV through early detection and initiation of ART. While models suggest high ART coverage would result in substantial declines in HIV incidence,[33, 34] empiric data from countries with population-level viral suppression exceeding 73% (e.g. Australia, eSwatini, and Thailand) have observed less significant reductions in HIV incidence relative to predictions from mathematical models.[35] Similarly, when high ART coverage was achieved in a series of cluster-randomized trials in sub-Saharan Africa, it resulted in decreased population-level HIV incidence; however, this decrease was insufficient to end HIV as a public health threat.[36–39] These discrepancies may in part be attributed to delayed diagnosis and ART initiation following infection,[40, 41] and gaps in the 95-95-95 targets for some population groups, for example young men and key populations. Additional barriers may include poor coverage of evidence-based prevention interventions and persistent structural barriers, particularly for key populations. More frequent HIV testing strategies could increase earlier diagnosis and initiation on ART and focusing testing and linkage efforts on key populations could reduce the access and coverage disparities in these groups. However, more frequent testing will also increase program costs, not only through additional commodity procurement but also for health systems, program coordination, and outreach. Policymakers may likely benefit from targeting limited testing resources towards high-risk groups such as key populations.

Dual RDTs may also increase syphilis testing frequency and coverage among key populations who are more likely to access HIV testing than testing for syphilis. Previous research has shown that coupling rapid syphilis testing in ANC may also increase HIV test coverage in LMICs, particularly in settings where HIV test coverage is low.[42] This strategy may be similarly effective at increasing test coverage for both diseases among key populations, as well as augment current ANC testing by reaching women in key populations who present late or are missed by ANC services. While there is a lack of data on dual RDTs among key populations, models of dual RDT during ANC have been shown to be cost-saving or cost-effective among both key populations and the general population of pregnant women.[7, 43] While dual RDTs are likely more effective in the context of ANC since testing can avert more adverse outcomes associated with congenital syphilis and mother-to-child HIV transmission, we find dual RDTs may also be cost-effective among non-pregnant key populations.

Our results are consistent with previously published models that show expanded testing and early access to ART for key populations in Viet Nam will cost-effectively reduce the country's HIV burden.[44, 45] Additionally, models from both low- and high-resource countries suggest HIV testing every 3-6 months among key populations can be cost-effective in concentrated epidemics.[46, 47] However, HIV risk within key populations is not homogenous; further targeting of higher-risk groups within key populations may be needed to achieve efficient testing regimens. While we examine the impact of increased testing frequency among key populations as a whole, previous research has described the benefits of targeting high-risk groups within key populations.[48] Individuals who engage in risky behaviors, such as those with more sexual partners, practicing unprotected sex, or needle/syringe sharing may benefit from additional testing or linkage to HIV prevention such as PrEP and harm reduction interventions. Further research is needed on the optimal testing intervals for higher-risk groups of key populations.

Globally, approximately one-third of key populations are not aware of their HIV status. Programs focusing on HIV testing and treatment among FSW and PWID in Viet Nam have shown success in reducing HIV prevalence in these groups; however, less than a third of MSM reported testing for HIV in 2015, likely

333 contributing to increases in HIV prevalence among this group in the past decade.[49] Annual syphilis testing among key populations in Viet Nam is similarly low, ranging from 16% among PWID to 36% among FSW.[18–20] Due to high dual prevalence of HIV and syphilis among key populations, dual testing is a promising strategy to increase testing coverage and linkage to care.

337 Our analysis has several limitations. We did not include the cost of scaling-up and training providers in administering dual RDTs. However, RDT are easy to use and can be administered by a lay provider, and rapid results can minimize loss to follow-up. Overall, dual RDTs have been shown to have adequate performance in field settings in Viet Nam among key populations.[50] Dual RDTs may also increase HIV test coverage as they can be easily conducted by community health workers outside of healthcare settings, and they may be more acceptable to some members of key populations who are concerned about stigma associated with testing.[51] Dual RDTs may also expand syphilis testing uptake, as most syphilis cases in Viet Nam are currently diagnosed at provincial hospitals. Despite this, some additional training, supervision, and support will be needed to scale-up dual RDT use among key populations.

346 We did not explicitly model HIV testing or diagnosis in this analysis as HIV testing uptake is not an adjustable model parameter in Spectrum. We instead modeled ART coverage, which required assumptions about the link between testing frequency and ART coverage. Since data on the impact of retesting on population HIV incidence is limited, we made conservative assumptions about the frequency of linkage to care and ART use following retesting. We assumed that HIV testing frequency would increase in Viet Nam among key populations in the baseline scenario but testing frequency would increase more quickly under the other scenarios. Because of this, we believe our estimates of the impact of increased testing frequency are conservative. Due to the lack of evidence on the impact of retesting on population HIV incidence, a model that explicitly includes testing rates as a parameter would also need to rely on assumptions concerning the relationship between testing behavior and ART enrollment.

Some model assumptions regarding the timing of HIV and syphilis testing may be inaccurate. Timing of testing is an important component from both a technical analytic perspective and guideline development process. In truth, there are a nearly limitless number of permutations of frequency and spacing of retests. We chose even spacing as it is easily interpretable at all levels of research, policy, and service delivery. This maximal spacing between tests is expected to have the largest impact at the population-level, assuming risk is evenly spread across the calendar year. We assume regular testing intervals for the entire population in each scenario, but it is possible – and entirely sensible – for people who had a risky sexual encounter or who are experiencing symptoms to seek more frequent retesting than biannually. We assumed in scenarios that included a dual RDT, additional syphilis screening tests would not be conducted. However, PLWH who know their status and present for syphilis screening do not need an HIV test.

We did not include the costs of outreach to achieve increased test coverage of key populations. Considerable expansions of first time testing among MSM in Viet Nam have recently been achieved through social media campaigns, perhaps providing a guide for cost-effectively increasing testing uptake among key populations.[49, 52] We also did not consider the burden that increased test coverage and frequency may have on the health system; however, as testing may be conducted effectively using lay providers, increased testing may not substantially impact the provision of other services.[51] Although targeting key populations in lower prevalence regions may be more difficult and costly, these results are robust to increased costs and it will likely remain an effective use of resources. Research that focuses on province-specific estimates of cost and impact would likely find that focusing on high-burden areas is more cost-effective; however, health policy, financing, guideline development, and implementation continue to be led nationally in Viet Nam. Therefore, national-level evidence is needed to direct decision making.

We assume that syphilis screening will not impact syphilis prevalence rates. Increased screening may reduce prevalence by increasing early treatment, but syphilis screening also has the potential to increase prevalence as individuals with latent syphilis are unlikely to transmit the infection to others unless they are treated and then infected again. Thus, we believe our estimates of infections averted and cost-effectiveness are conservative. Finally, there is limited data on population size, HIV and syphilis prevalence, and health seeking behaviors among key populations. We based our model input on estimates included in published literature as well as Viet Nam country sources.

CONCLUSIONS

Our study suggests that annual or biannual HIV and syphilis testing among key populations in Viet Nam using a dual RDT will increase HIV and syphilis detection and treatment, while remaining cost-saving or cost-effective. Integrating HIV and other STI testing can streamline services as well as expand testing and help countries with epidemics concentrated in key populations reach 95-95-95 targets. Future collection of empirical data, including conducting budget impact studies, would be useful to determine the impact of HIV and syphilis screening among key populations on ART uptake as well as HIV and syphilis incidence, particularly in concentrated HIV epidemics.

COMPETING INTERESTS

The authors declare no competing interests.

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CONTRIBUTORSHIP STATEMENT

CJ and AD devised the project and the main conceptual ideas. DC, DG, and RB parameterized the model.

DC and DG carried out the model implementation. VN and SVH provided model feedback. All authors, including DC, DG, RB, MS, MBD, MSJ, RB, MNO, VM, VN, SVH, MMT, TEW, CJ, and AD, provided critical feedback and helped shape the research, analysis, and manuscript.

DATA SHARING STATEMENT

Extra data is available by emailing David Coomes, dcoomes@uw.edu

ETHICS APPROVAL

This study did not receive nor require ethics approval as it does not involve human or animal participants.

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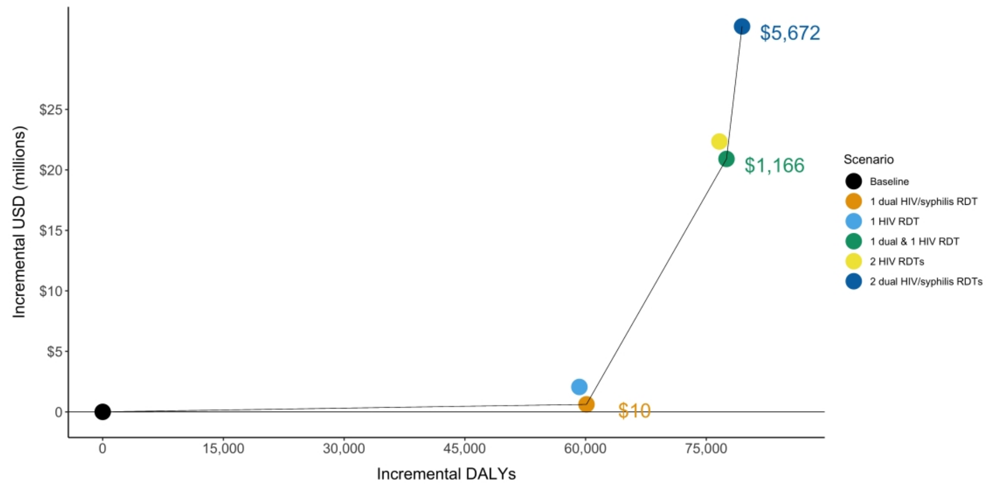
FIGURE LEGENDS

Figure 1. Efficiency frontier presenting the total disability adjusted life years (DALYs) and costs for five testing scenarios among key populations. The solid line indicates the scenarios that are not dominated by other scenarios. Dominated indicates that a scenario is either more costly and less effective or has a higher ICER than a scenario that is more effective. The ICERs for the non-dominated scenarios are shown. DALYs=disability adjusted life-years, ICER=incremental cost-effectiveness ratio, RDT=rapid diagnostic test, USD=United States dollars

Figure 2. Sensitivity analysis of non-dominated scenarios using a Monte Carlo simulation of the cost effectiveness of HIV/syphilis dual testing among key populations in Viet Nam. Plot shows 10,000 iterations in which 17 key parameters were randomly adjusted. All points below the green line are cost-effective at $2,715 per DALY averted and those below the solid black line (y-intercept) are cost-saving. Only non-dominated scenarios are shown in this figure; cost-effectiveness of *1 Dual Test* is compared to baseline, *1 HIV Test & 1 Dual Test* is compared to *1 Dual Test*, and *2 Dual Tests* is compared to *1 HIV Test & 1 Dual Test*. DALYs=disability adjusted life-years, ICER=incremental cost-effectiveness ratio, RDT=rapid diagnostic test, USD=United States dollars.



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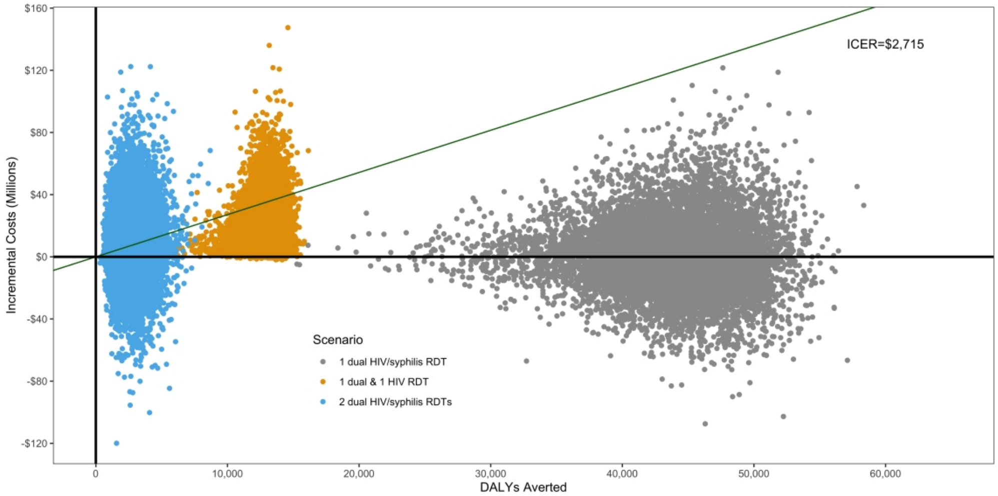

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Cost-effectiveness of implementing HIV and HIV/syphilis dual testing among key populations in Viet Nam: a modeling analysis

Supplemental material

Table S1: Parameters and probability distributions for Monte Carlo simulation

Table S2: Sensitivity analysis of all scenarios using a Monte Carlo simulation

Figure S1: Estimated yearly HIV incidence under baseline, annual, and biannual HIV testing

Figure S2: Cost pressure analysis of testing scenarios

Table S1. Parameters and probability distributions for Monte Carlo simulation. Table shows the baseline model parameter values and the probability distributions used for random draws of 17 variables for 10,000 Monte Carlo simulations. Beta distributions were used for all proportion parameters. For the beta distribution, the alpha and beta parameters were calculated as the baseline value multiplied by 100, except for the *impact* parameter where an alpha and beta of 25 was used. Gamma distributions were used for all other parameters. For the gamma distribution, the alpha parameter was calculated as the square of the baseline parameter divided by the square of the standard deviation. The beta parameter was calculated as the square of the standard deviation divided by the baseline parameter.

Model Parameter	Baseline value	Distribution	St. Dev	alpha/beta
Baseline HIV test acceptance	50%	Beta	N/A	50
Recommended test acceptance	75%	Beta	N/A	75
Additional test drop off rate	10%	Beta	N/A	10
HIV Lay Test Cost	\$4.50	Gamma	\$3.00	N/A
Syphilis RPR1 Cost	\$6.28	Gamma	\$3.50	N/A
Syphilis TPHA Cost	\$10.26	Gamma	\$5.00	N/A
HIV/Syphilis Dual Test Cost	\$6.50	Gamma	\$3.50	N/A
ART Treatment Cost	\$285	Gamma	\$50	N/A
Syphilis Treatment Cost	\$6.50	Gamma	\$3.50	N/A
Avg Years on ART	25	Gamma	3	N/A
Time Horizon	2035	Gamma	3	N/A
Impact	100%	Beta	N/A	25
Baseline Syphilis test acceptance FSW	35%	Beta	N/A	35
Baseline syphilis test acceptance MSM	27%	Beta	N/A	27
Baseline syphilis test acceptance PWID	16%	Beta	N/A	16
Baseline syphilis prevalence FSW	2.1%	Beta	N/A	2.1
Baseline syphilis prevalence MSM	6.7%	Beta	N/A	6.7
Baseline syphilis prevalence PWID	0.3%	Beta	N/A	0.3

Table S2. Sensitivity analysis of all scenarios using a Monte Carlo simulation. Table shows the percentage of simulations (10,000 iterations) in which each scenario is cost-effective (at $500 or $2,715 per DALY averted), cost-saving, or less-effective. Less effective scenarios are both less effective and more costly as compared to the scenario above. Scenarios are arranged in order of increasing cost and each scenario is compared to the one immediately above; 1 Dual HIV/syphilis RDT is compared to the baseline scenario.

Scenario	Cost-effective ($500)	Cost-effective ($2,715)	Cost-saving	Less effective
1 Dual HIV/syphilis RDT	85%	100%	52%	0%
1 HIV RDT	1%	1%	1%	98%
1 Dual HIV/syphilis RDT & 1 HIV RDT	32%	84%	18%	0%
2 HIV RDTs	1%	1%	1%	98%
2 Dual HIV/syphilis RDTs	45%	52%	44%	0%

DALY=disability adjusted life-year, RDT=rapid diagnostic test

Figure S1. Estimated yearly HIV incidence under baseline, annual, and biannual HIV testing. Figure shows modeled incidence under each scenario for the entire adult population of Viet Nam. The baseline scenario assumes 95% ART coverage among PLWH by 2028 (4.8% increase per year). Annual HIV testing models a 6.0% ART coverage increase per year, and biannual testing models a 7.2% ART coverage increase per year. Maximum test coverage is 95% for each model. All models assume ART coverage of 66% of men and 72% of women living with HIV in 2020. Scenarios are implemented in 2020 and modeled through 2035.

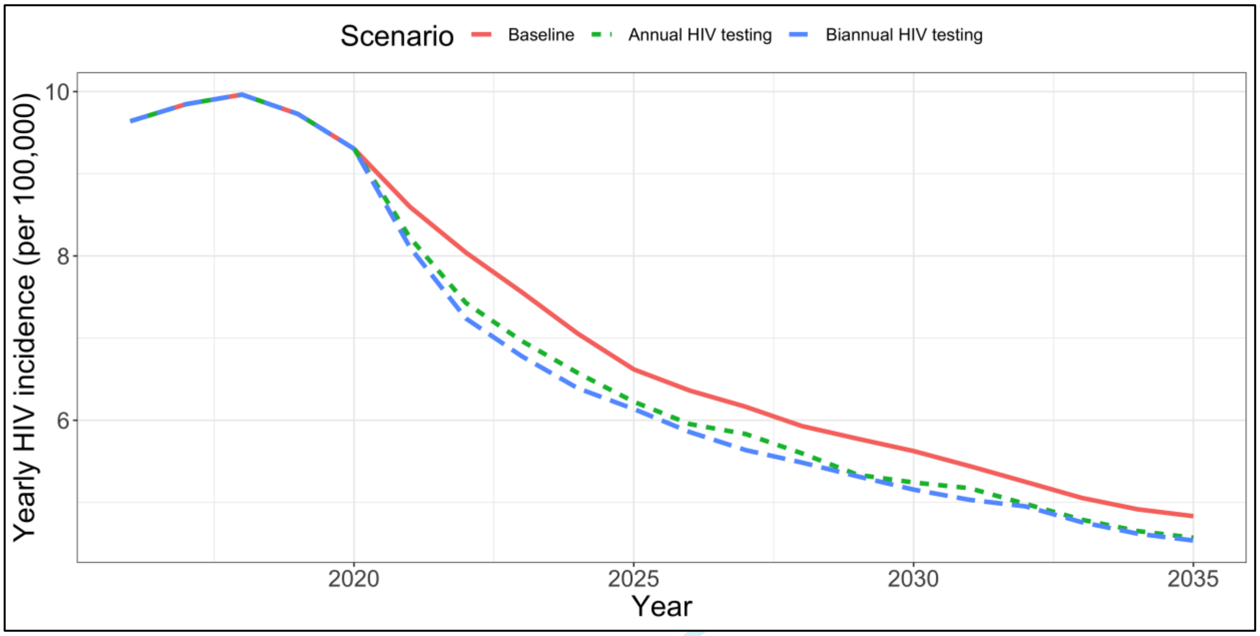
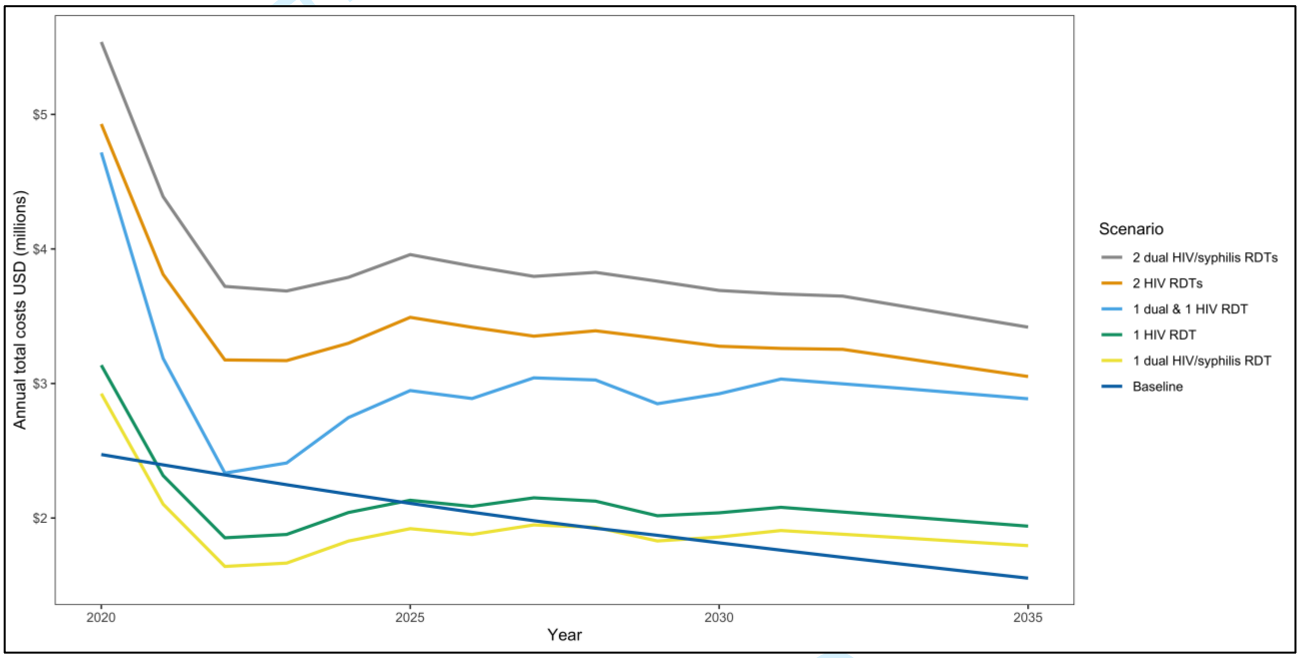


Figure S2. Cost pressure analysis of testing scenarios. Figure shows the discounted cost over time of each scenario. Costs are discounted 3% with a time horizon from 2020 – 2035. Baseline costs include testing costs assuming that 50% of key populations are tested for HIV each year and syphilis testing rates are specific to each sub-population (FSW, MSM, and PWID), and syphilis treatment costs. All other scenarios include the cost of HIV treatment averted compared to the baseline scenario, testing costs, and syphilis treatment costs. Scenarios including one test per year assume a 75% test acceptance rate, and those that include two tests per year assume a 75% test acceptance rate for the first test, and a 68.5% test acceptance rate for the second test. Each scenario refers to the number of tests per year. RDT=rapid diagnostic test, USD=United States dollars



CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Line 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Page 4
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 4 - 5
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 4
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 6-7
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 7
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Line 165
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Line 166
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Line 164
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	NA

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Page 6
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Line 110
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	NA
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Page 6
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 6
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 6
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Page 7-8
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Page 8
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 1
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 the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 3
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	NA

		of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Page 10
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	NA
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Page 10-14
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 14
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Page 14

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

The citation for the CHEERS Task Force Report is:

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