How to make HIV vertical transmission prevention good value for money in settings with very low HIV prevalence? Using economic evaluation guiding policy in the Philippines

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Abstract

Background: Preventing mother-to-child transmission of human immunodeficiency virus is important due to the impact of the disease to the women and their children's health. Established guidelines have recommended strengthening the ability to detect and treat HIV as early as possible. This study attempts to explore cost-effective PMTCT interventions in a low incidence, low-middle income setting such as the Philippines that can be replicated in other similar country settings.

Methods: The study utilized a model-based cost-effectiveness analysis through a decision tree analysis. The decision tree reflected the first ANC visit of a pregnant woman in the Philippines. Vertical transmission program was explored as ten possible PMTCT policy strategies including *Do-nothing* approach; status quo approach, which had 9% HIV testing, provision of tenofovir-based ART and neonatal prophylaxis, and automatic cesarean section; Eight universal screening policy strategies, which had 100% HIV testing and counselling, provision of tenofovir-based ART and neonatal prophylaxis with inclusion or exclusion of raltegravir for aggressive late antenatal care (ANC) HIV treatment on top of the ART given, breastfeeding or provision of substitute feeding, and normal delivery or cesarean section delivery

Results: Base case analysis revealed that policy strategy of universal HIV screening, with additional provision of raltegravir on those receiving late antiretroviral therapy, neonatal prophylaxis, and substitute feeding on normal delivery (urndnpsf) had the lowest ICER values among all policy strategies compared to status quo (₱291,170.26/QALY) and do nothing (₱291,710.26/QALY). Through universal screening coverage, at least 91% of the HIV cases in newborn may be averted. Cost of HIV test must be reduced by at least 45% to have a cost-effective PMTCT program. Alternatively, by performing group pre-test HIV counselling of at least three persons per session, the program will become cost-effective when compared to the unofficial Philippine threshold of ₱150,000/QALY.

Conclusions: Model design on HIV testing among pregnant women allows exploration of costs and outcomes of PMTCT interventions that focused on a low prevalence, low-middle income setting. From the study, HIV testing can be a major cost constraint for PMTCT. Furthermore, by performing group pre-test HIV counselling instead of per individual, a cost-effective PMTCT program may be achieved.

Background

World Health Organization (WHO) Global Health Observatory (GHO) data states there were 1.3 million pregnant women living with HIV in 2018, all of whom needed interventions for preventing mother-to-child transmission (PMTCT) of human immunodeficiency virus (HIV). It is estimated in 2018 that there were 160,000 newly HIV infected children recorded, 86% of which were in the African Region [1]. Both having HIV and being pregnant have increased susceptibility to opportunistic infections and other communicable diseases. Therefore, it is important to manage and reduce mother-to-child HIV transmission since the disease affect their own wellbeing and their children's health. Even if almost all low and middle income countries have already implemented lifelong ART treatment beginning immediately at diagnosis by mid 2019, promoting HIV screening during pregnancy should be strengthened to be able to detect and treat HIV as early as possible [1].

Published globally recognized clinical practice guidelines (CPGs) regarding PMTCT state that all pregnant women must get screened for HIV as early as possible during each pregnancy as part of the routine panel of prenatal screening tests [2]–[6]. Through this approach, all pregnant women will be provided to HIV test unless they explicitly decline. Guidelines emphasized early screening leads to early detection and early treatment of HIV [5].

Aside from CPGs, numerous cost-effectiveness analysis (CEA) studies on HIV screening in pregnant women have been conducted. A systematic review of similar CEAs was published in 2018, which included countries with varying income and prevalence of HIV. Generally, the universal screening program was cost-effective especially among countries with increasing HIV prevalence, however, the results should be interpreted with caution as countries used different threshold values. Moreover, dynamic changes in parameters that affect the models used in the studies may affect the reliability of the results 5–10 years from the present [7].

The Philippines, which is considered as low-middle income class, has considerably lower HIV prevalence among pregnant women compared to Cambodia, Thailand, Vietnam, and to other African countries [8]. It is estimated that less than 500 pregnant women need antiretrovirals for PMTCT, which is around 0.03% of the annual pregnant women population [9], [10]. However, presently, the country has one of the fastest growing HIV epidemics in the world with more than 70,000 cases of HIV to date. Only 16% of those women are provided with antiretroviral treatment and only 4% of the newborn cases are considered as early diagnosis [11]. A key step for the government to address the growing epidemic is to provide coverage from HIV screening, which includes testing and counselling, to

necessary treatment in order to prevent the transmission of HIV to the newborn as demonstrated by Thailand and Malaysia, which have recently achieved elimination of mother-to-child transmission of HIV last 2016 and 2018 respectively [12], [13]. This study attempts to design cost-effective PMTCT interventions in a low incidence, low-middle income setting such as the Philippines that can be replicated in other similar country setting.

Methods

Modelling approach

The study utilized a model-based cost-effectiveness analysis (CEA) from the perspective of the government healthcare system. A CEA is defined as a comparative analysis of alternatives, in terms of both their costs and outcomes. Government healthcare system perspective explored the interventions that should be paid by the government in order to provide continuum of care to the HIV-confirmed patients. Cost of each PMTCT policy strategy are estimated, relative to their benefits or outcomes, which are identified as quality-adjusted life-years (QALY). The model simulated a one-year one-time HIV testing and counselling of pregnant women considering the lifetime consequences of the pediatric HIV to calculate the costs and quality-adjusted life-years (QALY) over time using the beta version of Plant-A-Tree, which is an open source Microsoft Excel® add-in for constructing decision trees for economic evaluations [Plant-A-Tree version 1.0 website: <http://www.gear4health.com/page/i/plant-a-tree>].

The decision tree developed as shown in Fig. 1 started with a cohort of HIV test naive pregnant women stratified to their definitive HIV status. Pregnant women may either have their first ANC in the early (≥ 6 weeks before delivery) or late (< 6 weeks) period. As part of the routine panel of test for their first ANC visit, an HIV testing and counselling may be performed to which they may accept or reject. For those who accepted the HIV test and tested positive, a vertical transmission program (VTP) which included PMTCT interventions was offered to which they may accept or decline. Pregnant women who received late ANC had the same branches as early ANC with varying probability parameters.

Ten PMTCT policy strategies being considered in the study that represented the VTP in the model as shown in Table 1. *Do-nothing* approach simulates the delivery of a pregnant woman, regardless of her HIV status. This would mean no HIV testing, no provision of tenofovir-based antiretroviral therapy (ART) among HIV-positive, normal delivery without neonatal prophylaxis and substitute feeding. Status quo or *ad hoc* approach refers to the current Philippine efforts on PMTCT. This includes less than 10% HIV testing and counselling among pregnant women, provision of tenofovir-based ART to all those tested positive and received subsequent neonatal prophylaxis to their newborn; automatic cesarean section for all HIV-positive pregnant women regardless of their duration of ART is performed; finally, substitute feeding was also not provided to these women.

Table 1
PMTCT policy strategies

Testing choice	Name	Description	Coverage of screening [SQ/U]	Percent coverage of screening	Provision of ART regimen	Aggressive treatment (+ RAL) on late ANC in HIV + pregnant screened [R]	Mode of delivery of HIV + pregnant screened [ND/CS]	Provision of neonatal prophylaxis among HIV + pregnant screened [NP]	Provision of substitute feeding for infant among HIV + pregnant screened [SF]
Testing choice 0	Do Nothing	Do Nothing	No screening	0%	no	none	normal delivery	none	none
Testing choice 1	SQ	Status Quo screening	Ad hoc / status quo	9%	yes	none	cesarean section	yes	none
Testing choice 2.1	UCSNP	Universal screening: cesarean section, neonatal prophylaxis	Universal	100%	yes	none	cesarean section	yes	none
Testing choice 3.1.1	URCSNP	Universal screening: raltegravir, cesarean section, neonatal prophylaxis	Universal	100%	yes	yes	cesarean section	yes	none
Testing choice 3.1.2	UCSNPSF	Universal screening: cesarean section, neonatal prophylaxis, substitute feeding	Universal	100%	yes	none	cesarean section	yes	yes
Testing choice 4.1	URCSNPSF	Universal screening: raltegravir, cesarean section, neonatal prophylaxis, substitute feeding	Universal	100%	yes	yes	cesarean section	yes	yes
Testing choice 2.2	UNDNP	Universal screening: normal delivery, neonatal prophylaxis	Universal	100%	yes	none	normal delivery	yes	none
Testing choice 3.2.1	URNDNP	Universal screening: raltegravir, normal delivery, neonatal prophylaxis	Universal	100%	yes	yes	normal delivery	yes	none

ART = antiretroviral regimen, RAL = raltegravir, ANC = antenatal care, HIV = human immunodeficiency virus, ND = normal delivery, CS = cesarean section, NP = neonatal prophylaxis, SF = substitute feeding

Testing choice	Name	Description	Coverage of screening [SQ/U]	Percent coverage of screening	Provision of ART regimen	Aggressive treatment (+ RAL) on late ANC in HIV + pregnant screened [R]	Mode of delivery of HIV + pregnant screened [ND/CS]	Provision of neonatal prophylaxis among HIV + pregnant screened [NP]	Provision of substitute feeding for infant among HIV + pregnant screened [SF]
Testing choice 3.2.2	UNDNPSF	Universal screening: normal delivery, neonatal prophylaxis, substitute feeding	Universal	100%	yes	none	normal delivery	yes	yes
Testing choice 4.2	URNDNPSF	Universal screening: raltegravir, normal delivery, neonatal prophylaxis, substitute feeding	Universal	100%	yes	yes	normal delivery	yes	yes
ART = antiretroviral regimen, RAL = raltegravir, ANC = antenatal care, HIV = human immunodeficiency virus, ND = normal delivery, CS = cesarean section, NP = neonatal prophylaxis, SF = substitute feeding									

Eight universal screening policy strategies was simulated in the study. All universal screening policy strategies had 100% HIV testing and counselling among pregnant women [abbreviation: U]. Tenofovir-based ART was given to all pregnant women who tested positive and received subsequent neonatal prophylaxis [abbreviation: NP] to their newborn. A total of eight combinations of interventions were considered through (1) inclusion or exclusion of raltegravir for aggressive late antenatal care (ANC) HIV treatment on top of the ART given [abbreviation: R], (2) breastfeeding or provision of substitute feeding [abbreviation: SF], and (3) altering the mode of delivery: normal delivery or cesarean section delivery [abbreviation: ND or CS].

Model Parameters

Input parameters used in the analysis are listed in Table 2.

Table 2
Input parameters for the decision tree model and their references

Parameters	Values (SE)	Distribution	Reference
Epidemiological			
Population of pregnant women	1,700,618 (1,700,618)	log-normal	(14)
Pregnant women living with HIV	422 (422)	-	(15)
% pregnant women who had first ANC > 6 weeks before delivery	0.96 (0.07)	beta	(17)
% pregnant women who had first ANC < 6 weeks before delivery	0.04	-	(17)
% status quo screening	9.16%	-	(10)
% universal screening	100%	-	
Life expectancy of healthy person in the Philippines	69.09	-	(15)
Life expectancy of HIV + infant with treatment	15	-	(33)
Life expectancy of HIV + infant without treatment	2	-	(33)
Intervention effects			
Probability of HIV transmission during pregnancy	0.1892 (0.0360)	beta	(18)
Probability of postnatal HIV transmission	0.1620 (0.0495)	beta	(19)
Probability of HIV transmission when pregnant woman received 1st line ART $\geq$ 4 weeks before delivery	0.2013 (0.0237)	beta	(20)
Probability of HIV transmission when pregnant woman received 1st line ART < 4 weeks before delivery	0.5331 (0.0680)	beta	(20)
Relative risk of HIV transmission when pregnant woman received 1st line ART with raltegravir intensification < 4 weeks before delivery	0.2715 (0.0346)	beta	(21)
Probability of HIV transmission when pregnant woman delivered vaginally and received 1st line ART > 4 weeks	0.0392 (0.0050)	beta	(22)
Relative risk of HIV transmission when pregnant women delivered through cesarean section compared to vaginal delivery	0.3584 (0.0740)	beta	(23)
Relative risk of HIV transmission when breastfeeding pregnant women received 1st line ART < 4 weeks versus no treatment	0.5392 (0.0688)	beta	(24)
Sensitivity of HIV tests	1.00 (0.0128)	-	Expert advice
Specificity of HIV tests	1.00 (0.0128)	-	Expert advice
Acceptance to vertical transmission program (VTP) for each policy strategy	0.95	-	Assumption
Utility values			
Utility value HIV-positive newborn on therapy	0.83 (0.1403)	beta	(25)
Utility value HIV-negative newborn	1.00	-	(26)
QALY of HIV-positive newborn	6.18	-	computed
QALY of HIV-negative newborn	28.31	-	computed
Cost			
HIV test session for HIV-negative	₱566.67 (566.67)	gamma	(28)

ANC = antenatal care; HIV = human immunodeficiency virus; ART = antiretroviral therapy; VTP = vertical transmission program; QALY = quality-adjusted life-years

Parameters	Values (SE)	Distribution	Reference
HIV test session for HIV-positive	₱1,920.83 (1920.83)	gamma	(28)
Outpatient HIV/AIDS treatment	₱3,918.54 (3918.54)	gamma	(28)
Lifetime pediatric HIV	₱542,974.18 (542974.18)	gamma	computed
Neonatal prophylaxis	₱156.55 (156.55)	gamma	(28)
Substitute feeding	₱3,798.31 (3798.31)	gamma	(30)
Cesarean section	₱19,000.00 (19000)	gamma	(32)
Raltegravir therapy	₱15,557.75 (15557.75)	gamma	(31)
Viral load count test (once)	₱2,658.33 (2658.33)	gamma	(28)
CD4 + test (once)	₱931.03 (931.03)	gamma	(28)
Discount rate	0.03	-	(29)
ANC = antenatal care; HIV = human immunodeficiency virus; ART = antiretroviral therapy; VTP = vertical transmission program; QALY = quality-adjusted life-years			

Epidemiological parameters

The annual population of pregnant women was obtained from the recorded number of live births in the latest Philippine Statistics Authority annual report dated 2017 [14]. Prevalence of pregnant women needing PMTCT was obtained from the Spectrum-AIDS Epidemic Model (AEM) estimates for 2019 provided by the Department of Health Epidemiology Bureau – HIV Center. Spectrum software is commonly utilized by countries and Joint United Nations Program on HIV/AIDS (UNAIDS) in identifying key HIV indicators using country-specific HIV surveillance, national surveys, case reports, and vital statistics [15], [16]. Distribution of first ANC visit of the pregnant women was retrieved from the most recent published Philippines National Demographic Health Survey [17]. As for the status quo screening coverage, HIV/AIDS & ART Registry of the Philippines (HARP), which was deemed the best available data, provided this parameter [10].

Intervention effects

Clinical outcomes for each PMTCT intervention were sourced through most relevant published systematic review, randomized clinical trial, or observational study [18]–[24]. Baseline HIV transmission was computed by the summation of the probability of HIV transmission during pregnancy and postnatal period [18], [19]. Due to limited studies that compared the efficacy of tenofovir (TDF) - based regimen with placebo on MTCT outcomes, the study by Hoffman et al. [20], which stratified the transmission rate depending on the duration of highly active antiretroviral therapy (HAART) intake during pregnancy period was used to determine efficacy of the ART regimen, regardless of the components of HAART regimen. To incorporate the efficacy of intensification of raltegravir for HIV detected during late pregnancy, values were computed through the data from published study conducted in Thailand on late-presenting HIV-positive high-risk pregnant women [21]. A study on HIV-positive pregnant women taking HAART from 2000–2011, that was stratified the outcomes based on the mode of delivery, determined the HIV transmission on greater than 4 weeks on ART with vaginal delivery [22]. Relative risk of HIV transmission of elective cesarean section delivery versus vagina delivery on HIV-positive pregnant women was determined through the systematic review by Kennedy et al. [23]. Also, it was also necessary to demonstrate the benefit of receiving ART

regimen less than 4 weeks before delivery in a breastfeeding population versus no treatment [24]. An assumption of 100% sensitivity and specificity for the HIV test was inputted as advised by expert panel.

HIV transmission rates for each scenario of the policy strategies were calculated as shown in Table 3. Scenario with the least possible HIV transmission rate, which was receiving early antiretroviral therapy with normal delivery on a breastfeeding population, resulted to 0.15% MTCT rate, whereas the highest HIV transmission rate of 35.12%, were those who did not receive any PMTCT interventions.

Table 3
HIV transmission rates for each possible combination of PMTCT interventions

				Transmission prenatal to delivery	Transmission postnatal	Total	
NO INTERVENTION				baseline	0.1892	0.1620	0.3512
Late ART	Normal Delivery	Breastfeeding	late	0.1009	0.0873		0.1882
Late ART	Cesarean Section	Breastfeeding	late	0.0361	0.0873		0.1235
Late ART + RAL	Cesarean Section	Breastfeeding	late	0.0184	0.0873		0.1058
Late ART + RAL	Normal Delivery	Breastfeeding	late	0.0184	0.0873		0.1058
Late ART	Normal Delivery	Substitute feeding	late	0.1009	0.0000		0.1009
Late ART	Cesarean Section	Substitute feeding	late	0.0361	0.0000		0.0361
Late ART + RAL	Cesarean Section	Substitute feeding	late	0.0184	0.0000		0.0184
Late ART + RAL	Normal Delivery	Substitute feeding	late	0.0184	0.0000		0.0184
Early ART	Normal Delivery	Breastfeeding	early	0.0015	0.0000		0.0015
ART = antiretroviral therapy; RAL = raltegravir							

Utility values

Assumption that utility values will be exclusive to HIV-positive or HIV-negative newborns was applied to the model. Utility value of HIV-positive newborn was adapted from the analysis of Sanders et al. [25]. The utility value for HIV-negative newborns, assumed to be healthy Filipino individuals, used the Philippine value set of EQ-5D-5L for 11111 [26]. A simple lifetime Markov model was simulated to determine the QALY of HIV-positive and HIV-negative newborns using Philippine life table and assigning those alive with utility value of 1 and dead as zero.

Cost parameters

Cost parameters utilized for the model included direct medical costs associated in providing PMTCT interventions to the pregnant women until delivery and lifetime horizon for HIV-positive newborns. All costs were presented in Philippine peso and adjusted to 2019 values adopting the methods previously discussed by Turner et al. [27].

Government procurement rates, whenever available, were obtained from the annual procurement report from the Department of Health [28]. Costs associated with providing HIV test for either HIV-positive or HIV-negative pregnant women were computed using activity-based costing validated with local HIV experts and hospital staff from the national HIV referral center. As for the lifetime pediatric HIV costs, the authors have calculated the value through a separate Markov model with discount rate of 3% [29]. Providing substitute feeding for 6 months to compensate the time period for exclusive breastfeeding was based on a local study on the economic burden of infant formula [30]. PhilHealth coverage was applied for cesarean section delivery while the cost of raltegravir, being not presently registered in the Philippine Food and Drug Administration, was adopted from a Thailand report [31], [32].

Analyses

First, the total program costs for each PMTCT policy strategy was compared with status quo and do nothing approach. Moreover, the incremental costs and incremental QALY compared with status quo and do nothing approach were calculated. Stratification of the total program costs into screening cost, PMTCT costs, and lifetime pediatric HIV costs were determined.

Second, the cost-effectiveness of each PMTCT policy strategy was assessed compared to status quo and to do nothing approach with an acceptance to the vertical transmission program strategies of 95%. The difference between the costs of each policy strategy with the do nothing approach or status quo over the difference between their utilities estimated the incremental cost-effectiveness ratios (ICERs). ICERs were compared to the unofficial set threshold of ₱150,000/QALY gained, country. This value is referenced in the previous guidelines of the Philippine National Formulary [33].

Third, univariate and probabilistic sensitivity analyses, through Bayesian framework, were carried out for all applicable parameters. Determining the major drivers for the change in the ICER values was performed through univariate sensitivity analysis on 95% confidence interval. A tornado diagram was generated to illustrate the parameters that elicit the most change to the ICER value. Next, probabilistic sensitivity analysis utilized Monte Carlo simulation using the parameters' appropriate probability distributions. Probability parameters bounded between the range of zero and one applied the beta distribution. Cost parameters, which yields only positive values, used the gamma distribution. Moreover, the population of pregnant women which is expected to have an additive natural growth processes was put under the log-normal distribution. All of the applicable parameters were sampled through the joint distribution and used to yield the costs and outcomes associated with each proposed policy option with 10,000 iterations. ICER values for each of the pair of cost and outcome results were calculated, then the cost-effectiveness acceptability curves and cost-effectiveness acceptability frontiers were generated.

Lastly, a post hoc two-way sensitivity analysis was performed by selecting two sensitive parameters from univariate sensitivity analysis that is predicted to change within the next five years. A head-to-head two-way sensitivity analysis was performed to determine the range of values of each parameter that will result to an ICER value of less than ₱150,000/QALY gained.

Results

Program costs consisted of cost of HIV screening, cost of providing tenofovir-based ART to the pregnant women, cost of nevirapine for the newborn for 6 weeks, cost of delivery (normal delivery, cesarean section), cost of providing substitute feeding for 6 months, and cost of lifetime pediatric HIV.

Majority of calculated program costs for the proposed policy strategies were dedicated for HIV screening costs, which was computed by the sum of costs of the HIV test kits and costs health worker performing pre- and post-test counseling. HIV screening costs for status quo screening was 45% of the total program cost whereas, HIV screening costs were 99% of the program cost proposed policy strategies. For the lifetime HIV consequences of the newborn, 45% of the program costs were dedicated for lifetime pediatric HIV treatment compared to 1% in universal screening policy strategies.

Tables 4 and 5. presented the cost-effectiveness analysis of the policy strategies in terms of ICERs in Philippine peso (₱) per QALY gained versus status quo screening and do nothing approach. The policy strategy of universal HIV screening, with the provision of raltegravir on those receiving late antiretroviral therapy, neonatal prophylaxis, and substitute feeding on normal delivery had the lowest ICER values among all proposed policy strategies (unrdnpsf). Furthermore, it yielded the least program costs with highest QALY gained among the proposed policy strategies. However, ICER values generated were higher than the unofficial PH threshold set at ₱150,000/QALY gained.

Table 4
Incremental costs, incremental QALY gained, and ICER (₱/QALY) of policy strategies against status quo screening

	Incremental program cost (₱)	Incremental QALY gained	ICER (₱/QALY)
ucsnp	₱802,892,921.13	2,717.46	295,457.17
urcsnp	₱802,987,041.19	2,723.69	294,815.88
ucsnpsf	₱802,200,277.48	2,748.15	291,905.90
urcsnpsf	₱802,294,397.54	2,754.38	291,279.78
undnp	₱803,149,139.18	2,694.72	298,045.12
urndnp	₱802,685,404.03	2,723.69	294,705.13
undnpsf	₱802,456,495.53	2,725.41	294,435.07
urndnpsf	₱801,992,760.38	2,754.38	291,170.26
u = universal HIV screening; r = raltegravir; cs = cesarean section; nd = normal delivery; np = neonatal prophylaxis; sf = substitute feeding; QALY = quality-adjusted life-years; ICER = incremental cost-effectiveness ratio			

Table 5
Incremental costs, incremental QALY gained, and ICER (₱/QALY) of policy strategies against do nothing approach

	Incremental program cost (₱)	Incremental QALY gained	ICER (₱/QALY)
ucsnp	₱884,561,526.25	2,992.33	295,610.05
urcsnp	₱884,655,646.32	2,998.56	295,027.22
ucsnpsf	₱883,868,882.60	3,023.01	292,380.12
urcsnpsf	₱883,963,002.67	3,029.24	291,809.84
undnp	₱884,817,744.30	2,969.59	297,959.62
urndnp	₱884,354,009.16	2,998.56	294,926.63
undnpsf	₱884,125,100.65	3,000.28	294,681.18
urndnpsf	₱883,661,365.51	3,029.24	291,710.26
u = universal HIV screening; r = raltegravir; cs = cesarean section; nd = normal delivery; np = neonatal prophylaxis; sf = substitute feeding; QALY = quality-adjusted life-years; ICER = incremental cost-effectiveness ratio			

Without PMTCT interventions, 147 out of 422 newborns will be born with HIV for the year. In the Philippines, where the status quo is around 9% HIV screening among pregnant women, the ad hoc HIV screening program on pregnant women will be able to prevent 13 more HIV cases compared to no screening. All proposed policy strategies for universal screening coverage, on the other hand, may prevent at least 134 out of the 147 HIV cases which is more than 91% of the total cases.

Figure 2. displays the results of the one-way sensitivity analysis to identify the effect of uncertainty of each input parameter in the cost-effectiveness analysis model. The analysis showed that specificity of the HIV test kits, quality of life of those born without HIV, the prevalence of HIV-positive pregnant women, cost of HIV screening with negative results, and the population of pregnant women in the country significantly change the ICER value. To achieve a lower ICER value, higher QALYs of the population, higher HIV prevalence among pregnant women, lowest HIV screening costs on HIV-negative pregnant women, and lower annual population of pregnant women in the country are desired. By reducing the cost of HIV tests among HIV-negative pregnant women by a minimum of 45%, the PMTCT policy strategy will become good value for money in the country.

The probabilistic sensitivity analysis on the ICER of the proposed policy strategy with the lowest ICER versus do nothing approach or status quo screening suggests that the strategy was 42% cost-effective when compared to the PH threshold as shown in Fig. 3. Willingness-to-pay (WTP) of at least ₱180,000/QALY gained will make the proposed policy strategy more value for money compared to status quo screening.

Post-hoc two-way sensitivity analysis on parameters of prevalence of HIV-positive pregnant women and cost of HIV screening among HIV-negative pregnant women were purposely selected as the most dynamic sensitive parameters based on the univariate sensitivity analysis. Adjustments on the parameters by introducing the concept of group HIV pre-test counselling, which will result to lower labor costs, were performed. The cost for each pre-test HIV counselling for HIV- pregnant women was calculated based on the number of persons per group counselling session (1–20 people), while the range of prevalence of pregnant women was estimated from Spectrum-AEM model. Figure 4. shows the optimum combination of these two parameters to have cost-effective results depending on the threshold value being compared. This shows that with increasing prevalence of pregnant women and decreasing the cost of HIV test, the lower the ICER will become. Incorporating the group pre-test HIV counselling from 1–20 persons per session approach, optimal number of persons per counselling session can be determined depending on the value of prevalence of pregnant women applied. In the case of the Philippine setting, with 422 pregnant women needing PMTCT, at least 3 persons per group HIV pre-test counselling will guarantee the program to become cost-effective.

Discussion

The study comprehensively evaluated a cost-effectiveness analysis of different program components in PMTCT which spanned from HIV counseling and testing to providing substitute feeding in a low incidence, low-middle income setting using Philippines as the case study. In addition, this is the first economic evaluation that analyzed combination of PMTCT interventions including raltegravir intensification for late ART and the first PMTCT economic evaluation done in the country. For countries intending to cover or update their coverage on the combination of PMTCT interventions, the study may assist them by illustrating a model template for HIV screening program among pregnant women.

From the country's perspective, HIV testing can be a major cost constraint for PMTCT. Reducing the cost of HIV test for HIV-negative pregnant women by 46% will be the most feasible option for the policy strategy to be cost-effective. Also, due to the expected rise in the prevalence of pregnant women needing PMTCT, the probability of the policy strategy to become good value for money will increase. It should also be taken consideration that the threshold used to compare the computed ICER values was around one Gross Domestic Product (GDP) per capita of the country, which was used in previous economic evaluations conducted in Philippine context as suggested in the Philippine National Formulary guidelines.

Twenty-one cost-effectiveness analyses included in the systematic review published by Bert et al. in 2018 had agreed on the cost-effectiveness of universal antenatal screening [7]. However, due to heterogenous characteristics of the countries and methodologies applied to the studies, several factors may have heavy influence on the results of the studies. These include perspective of the study, interventions used for the policy strategy, HIV prevalence per country, and the income level of country setting, which may determine the threshold used to compare the ICER value.

Perspectives used by similar studies conducted may be simply classified either societal, which included the PMTCT costs along with lifetime costs for the HIV-positive women and the perinatally infected newborns, or government payer, where the focus was mostly providing PMTCT and treatment only to the infected newborn [7]. Government payer perspective may underestimate the benefit of providing the universal HIV test due to several reasons. First, the detection of HIV among pregnant women may prompt additional detection among their respective partners as well as prevent further transmission of HIV on their succeeding pregnancies. In fact, according to the study of Kendall [34], the most promising opportunity of women to determine their HIV status is during their pregnancy. When the pregnant women were not diagnosed during their ANC, the most probable next event that would trigger seeking relevant care will be during their own experiences AIDS-related complications or those of a close family member's. Time period for providing appropriate care for HIV is critical to prevent HIV perinatal transmission. Therefore, HIV diagnosis must be performed as early as possible, wherein ANC visit may serve as a good entry point for any country setting [5]. Prevention of addressing more progressed stages of HIV that would incur additional costs and decrease their overall QALYs were not accounted in government payer perspective. Second, the consequences on the women after delivery due to cesarean section was not assessed. These include higher rates of infectious complications and surgical traumas, longer hospital stay and in-hospital deaths [35]. Although it is proven on systematic reviews that cesarean section provides less risk of maternal HIV transmission, the consequences of maternal injuries were not included in the payer's perspective. Third, by including only the lifetime treatment costs of infected newborns, the productivity contribution of these population due to increased lifetime was also not considered.

The interventions used in the PMTCT policy strategies of the studies included in the systematic review contained a screening strategy (universal or targeted), with ART and prophylaxis to the newborn with or without considering the health of the woman after her labor [7].

Although most of the studies included considered retesting during late pregnancies, which was not considered in this study, none had investigated the addition of raltegravir as an additional intervention during HIV detection in late pregnancies. The published study by Puthanakit et al. conducted in Thailand showed that providing raltegravir on top of the standard of care for those diagnosed with HIV on late pregnancies drastically reduces the risk of perinatal HIV transmission [21]. This finding was deemed significant in the development of the optimal PMTCT policy strategy. Furthermore, the conducted study was novel in terms of considering how to design an appropriate and feasible PMTCT policy strategy for any country setting who will start to publicly cover PMTCT interventions.

The national prevalence from passive surveillance of HIV-positive pregnant women in the Philippines is around 0.0248% in 2019, which is considered as *low prevalence* according to UNAIDS [9], [36]. This level of prevalence is comparable to Australia, New Zealand, and Hong Kong but has lower prevalence compared to India, Thailand, Uganda, and South Africa [4], [37]–[42]. All of these countries included suggested that PMTCT interventions including universal HIV screening among pregnant women is cost-effective in their respective country setting [7]. As determined in the univariate sensitivity analysis, prevalence was identified parameters that has great influence on the ICER value. Higher prevalence, with similar income levels and threshold level utilized, would easily make the PMTCT policy strategy good value for money, especially since the prevalence in those countries is higher than the Philippines, with ranges from 1.63–19.5% [38], [39], [41], [43]. However, those countries with comparable prevalence with the Philippines were high income countries and had a much greater threshold used to compare with their ICER values [44]. Compared to the PH threshold of ₱150,000/QALY gained, which is around US\$3,000, high-prevalence countries used the estimate values US\$17,600, US\$24,000, US\$10,100 for New Zealand, Australia, and Hong Kong respectively as thresholds for good value of money [37], [40], [41].

Among the sensitive parameters in the univariate sensitivity analysis, the cost of HIV screening can be adjusted by the government payer. One method that was performed in the study is group HIV pre-test counseling, in order to reduce the total amount of time spent of the health worker for counselling, as well as to address the foreseen insufficiency on the number of health workers available. According to the WHO Guidance on testing and counselling for HIV, in order to improve access, a combination of group health information talks to be followed by individual risk based assessments tailored to the patient's HIV status is a valid method to find a balance between complicated and overdrawn counselling sessions and rapid, intense education/information transfer [45]. As demonstrated in the study, for the case of Philippines, a group HIV pre-testing counselling of at least three persons per session will make the PMTCT policy strategy cost-effective. To add, communities with limited number of health workers may benefit the most of this technique by organizing health information sessions attended by all the people in the community [46]. Also, the local HIV patient group in the Philippines have stated that their organization have trained their members to become qualified peer HIV counselors in order to supplement the lack of health workers proficient in HIV counselling in the country.

The study has its limitations whenever it will be used as a model template for countries that will consider coverage of HIV test among pregnant women. First, several assumptions on the input parameters were made due to unavailability of specific data needed. By assuming equal efficacy of treatment regimens described in Hoffman et al, with the HAART regimens listed current WHO, guidelines may underestimate the benefits gained by reducing the rate of MTCT due to HAART alone [13], [20]. Adaptation and adjustments of foreign data on the utility values of HIV-infected newborns, cost of raltegravir, and lifetime costs of providing treatment for HIV-positive newborns were due to absence of local studies. Second, only direct medical costs were considered in the study. Accounting for productivity costs (e.g. cost of sick leaves and hospitalizations due to HIV complications) and the direct non-medical costs (e.g. travel cost) along with inclusion of costs of adverse events due to treatment regimens in the course of pregnancy, treatment costs of long term side effects to the women and children receiving PMTCT interventions and ARV resistant women and children may provide truer estimate of costs and benefits. Third, the study also did not account for the additional benefits due to early HIV detection and treatment including the prevention of MTCT on succeeding pregnancies, as well as slowing down disease progression of women and their partners. Fourth, any cultural or social factors that may indirectly contribute to the costs and benefits of the program was not explored. To illustrate, published studies from Uganda and England, revealed that HIV patients travel significantly farther to access healthcare than those without HIV. Factors may include lack of necessary specialty services, supply of ART, and possibly to protect confidentiality [47], [48]. Therefore, local feasibility studies must supplement before actual program implementation to determine other technical, political, economic or practical barriers that may impede the operation of the HIV testing program.

HIV/AIDS is not just a health problem, the spread of this infectious disease is highly correlated with socioeconomic, environmental and ecological factors such as population growth, environmental and land-use changes, changing human behaviors and political reorganizations [1]. The research conducted illustrated novel ways how to design cost-effective PMTCT policy strategies in a low income and low prevalence setting. By introducing adjustment methods of the parameters, these imply that for countries with low prevalence, PMTCT strategies coverage may be implemented accordingly. The recognition of maternal HIV transmission as a public

health concern in the country must trigger the implementation of PMTCT policies. In such cases where there are underreporting of HIV cases along with the uncontrollable rise in the number of in the Philippines as mentioned by local expert consultations, the consideration for a full-scale implementation of PMTCT must be realized. Furthermore, although the research used scenarios based on actual global practices, outdated practice such as performing cesarean section on HIV-positive pregnant women, regardless of their viral load levels should be discontinued [49]. Knowledge on the recent clinical protocols on the criteria for cesarean section must be enforced.

Conclusions

The model design on HIV testing among pregnant women allowed exploration of costs and outcomes of PMTCT interventions that focused on a low prevalence, low-middle income setting. From the study, HIV testing can be a major cost constraint for PMTCT. Furthermore, strategies that will affect sensitive parameters like by performing group pre-test HIV counselling instead of per individual may result to a cost-effective PMTCT program, even at low prevalence, low income setting.

List Of Abbreviations

PMTCT: prevention of mother to child transmission; HIV: human immunodeficiency virus; ART: antiretroviral therapy; ANC: antenatal care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-years; WHO: World Health Organization; GH0: Global Health Observatory; CPGs: clinical practice guidelines; CEA: cost-effectiveness analysis; AEM: AIDS epidemic model; UNAIDS: United Nations Program on HIV/AIDS; HARP: HIV/AIDS & ART Registry of the Philippines; TDF: tenofovir; HAART: highly active antiretroviral therapy.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The raw data and all necessary calculation are found on the excel file submitted along with this manuscript with file name of [HIV Model 2020 copy.xlsm]

Competing Interests

The authors declare that they have no competing interests.

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Authors' contributions

GDU, DBB and YT designed the study, developed and refined the model. GDU collected the data. DBB, ACL and YT provided technical expertise on the parameters, use of the model and ensured overall quality of the study. GDU performed the analysis, constructed the tables and figures, and interpreted the data and results of the drafted manuscript. All authors contributed to the final draft of the manuscript and gave final approval of the version to be published.

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Figures

Figure 1

Decision tree model for the study

Figure 2

One-way sensitivity analysis (top 11 most sensitive parameters)