Emtricitabine + Tenofovir Disoproxil Fumarate fixed-dose combination as Oral Pre-Exposure Prophylaxis (PrEP) **to reduce the risk of sexually acquired HIV infection**

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List of Abbreviations

DOH	Department of Health - Philippines
EB	Epidemiology Bureau
PNF	Philippine National Formulary
NASPCP	National AIDS and STI Prevention and Control Program
WHO	World Health Organization
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
RCT	Randomized clinical trials
PrEP	Pre-Exposure Prophylaxis
HIV	Human Immunodeficiency Virus
PLHIV	People living with HIV
FDC	Fixed-Dose Combination
U=U	Undetectable = Untransmittable
TDF	Tenofovir disoproxil fumarate
TFV	Tenofovir
TFV-DP	Tenofovir diphosphate
NPI	Non-pharmacologic interventions
DALY	Disability-adjusted life year
IDU	Injection drug users
ART	Antiretroviral therapy
MMT	Methadone maintenance treatment
MSM	Men having sex with other men
TW	Transwomen
PWID	People who inject drugs
CAS	Condomless anal sex
GEE	Generalized estimating equation

Definition of Terms

TERM	DEFINITION
Acquired Immuno-Deficiency Syndrome (AIDS)	A complication of HIV infection in which there is marked progressive failure of the immune system. This condition often leads to fatal opportunistic infections (e.g., toxoplasmosis) and cancers (e.g., Kaposi's sarcoma).
Antiretroviral Therapy / Treatment (ART)	Medication used to control HIV/AIDS by slowing down HIV replication
Chemsex	refers to the use of psychoactive substances (i.e., GHB/GBL and synthetic cathinones) during any sexual activity.
Cisgender	Individuals whose personal identity is congruent with their sex at birth.
Human Immuno-Deficiency Virus (HIV)	A virus that attacks the immune system.
Men Having Sex with Men (MSM)	Men who perform any sexual activity with individuals of the same sex at birth, regardless of their SOGIE. They may include: ● Straight men who have sex with other men for money or to satisfy their sexual needs ● Gay or bisexual men who have sex with other men
Persons Living with HIV (PLHIV)	Individuals who were infected and remained positive for HIV
Postexposure Prophylaxis for HIV (HIV PEP)	Refers to the pharmacologic treatment(s) given after sexual contact aimed at preventing HIV infection
Pre-Exposure Prophylaxis for HIV (HIV PrEP)	Refers to the pharmacologic treatment(s) given prior to sexual contact aimed at preventing HIV infection
Serodiscordant couples	Couples in which one individual is HIV-positive and the other is HIV-negative
Slamming	The act of injecting intravenous psychoactive drugs prior to engaging in sex.
SOGIE	Sexual Orientation, Gender Identity, and Expression
Sexual Orientation	An individual's pattern of romantic/sexual attraction (e.g., straight, bisexual, gay/lesbian, asexual)
Gender Identity	A person's sense of their own gender (e.g., man, woman, transman, transwoman, non-binary)
Gender Expression	A person's behavior, appearance, or interests conforming with the

	society's expectation of what a specific gender is (e.g., masculine, feminine, androgynous)
The Sexually Marginalized	Include people whose sexuality differs from the heteronormative expectations of the society
Sexually Transmitted Infections (STI)	Diseases acquired through sexual contact
Transgender	Individuals whose personal identity is not congruent with their sex at birth (i.e., transmen or transwomen).

Background

What is HIV?

The human immunodeficiency virus (HIV) is a viral infection that targets the immune system and weakens people's defenses against many infections and some types of cancer. The virus destroys and impairs the function of immune cells, causing infected individuals to gradually become immunodeficient. It can be transmitted via exchange of a variety of body fluids from infected people such as blood, breast milk, semen and vaginal secretions (WHO, 2020). The risk of acquiring HIV is 26 times higher among men having sex with other men (MSM), 29 times higher among people who inject drugs (PWID), 30 times higher for people who exchange sex for money or non-monetary items, and 13 times higher for transwomen (TW) (UN AIDS Fact sheet, 2020). HIV, if left untreated, can progress to Acquired Immune Deficiency Syndrome (AIDS).

AIDS is the late stage of HIV infection, which occurs when the body's immune system is severely incapacitated due to the effects of the virus. A person with HIV is considered to have progressed to AIDS when (1) the number of CD4 cells falls below 200 cell/mm^3 or (2) they develop one or more opportunistic infections regardless of their CD4 count (hiv.gov). Without HIV treatment, people with AIDS typically survive about three years, however, once someone develops opportunistic illnesses, life expectancy without treatment falls to about one year. HIV and AIDS treatment involve taking antiretroviral therapy (ART) which reduces HIV viral load.

What is the current standard of care?

International Guidelines

In 2013, the WHO published the first consolidated guidelines on the use of antiretroviral (ARV) drugs for HIV treatment and prevention across all age groups and populations. In this guideline, two key recommendations were introduced: *(1) Antiretroviral therapy (ART) should be initiated in everyone living with HIV at any CD4 cell count*; and *(2) the use of daily oral pre-exposure prophylaxis (PrEP) which contains emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg fixed-dose combination (FDC) is recommended as a prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches*. The second recommendation is based on clinical trial results confirming the efficacy of the ARV drug tenofovir (TDF) for use as oral PrEP to prevent people from acquiring HIV in a wide variety of settings and populations. In the 2013 WHO

recommendation for oral PrEP, the recommended target population with substantial risk included serodiscordant couples, MSM and TW.

In 2015, the WHO reissued the recommendation for oral PrEP, specifically containing tenofovir disoproxil fumarate (TDF), that should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of a combination HIV prevention approach. Compared to the 2013 recommendation, the 2015 guideline further expands the target population which now covers "some groups of MSM, TW in many settings and heterosexual men and women who have sexual partners with undiagnosed or untreated HIV infection" (WHO, 2015) as well as any individual with *substantial risk of acquiring HIV*–defiined by WHO as HIV incidence greater than 3 per 100 person-years in the absence of PrEP.

In July 2021, the WHO published an updated guideline on HIV entitled *Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring: Recommendations for a Public Health Approach*. The recommendation to use oral PrEP (tenofovir disoproxil fumarate 300 mg + emtricitabine 200 mg FDC) from the previous guideline did not change except for the expansion of the target population to cover cisgender MSM. Other recommendations for oral PrEP as an adjunct to other HIV prevention strategies included (1) self-testing on HIV, which resulted in negative, needs immediate further testing if a client is to start using oral PrEP (strong recommendation, high certainty evidence); and (2) among women, oral PrEP regimens may be added to the use of dapivirine vaginal rings (*conditional recommendation, moderate-certainty evidence*). Lastly, the WHO issued a statement on the safety of oral PrEP on pregnancy and breastfeeding: "*An increasing body of evidence has demonstrated that TDF-containing oral PrEP is safe during pregnancy and breastfeeding*".

Local Guidelines

The Philippine National AIDS and STI Prevention and Control Program (NASPCP) and the Philippine National AIDS Council currently provide combination prevention strategies consisting of providing condoms, lubes, HIV education, counseling and screening. As per DOH Memorandum Circular 2019-0038, otherwise known as the Implementing Rules and Regulations of Republic Act No. 11166 entitled "Philippine HIV and AIDS Policy Act", education and prevention programs for HIV and AIDS included the following:

1. Safer sex practices among the general population, including sexual abstinence, sexual fidelity, and consistent and correct use of condom especially among key populations;
2. Other practices that reduce risk of HIV infection;
3. Universal awareness of and access to evidence-based and relevant information and education, and medically safe, legally affordable, effective and quality treatment; and
4. Knowledge of the health, civil, political, economic and social rights of PLHIV and their families.

In 2018, Project PREPPY (PrEP Pilipinas) was launched by Love Yourself, Inc., an AIDS advocacy group providing health services related to HIV. In this 24-month pilot project, the organization introduced daily oral PrEP (emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg) in fixed-dose combination (FDC) in its array of HIV-related health services. This project was supported by the RITM and the DOH. Currently distributed oral PrEP (emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg FDC) in the Philippines was donated by Global Fund to Fight AIDS, TB, and Malaria because it is not yet listed in the Philippine National Formulary (PNF). The pilot project was a community-based delivery preventive HIV pre-exposure prophylaxis for MSM and TW at high risk of acquiring HIV infection (WHO, 2020b).In January 4, 2021, the DOH released Department Memo 2021-0017 with subject title *Interim Guidelines on Pre-Exposure Prophylaxis (PrEP) for the Prevention of HIV infection in the Philippines* with the objective to provide details on the delivery of PrEP services for people at substantial risk of HIV infection.

With the addition of the use of oral PrEP (tenofovir disoproxil fumarate 300 mg + emtricitabine 200 mg FDC), the NASPCP further adds the following specific activities related to the mandated prevention programs:

1. Advocacy of undetectable = untransmittable (U=U) messaging
    - U=U refers to the concept that people living with HIV (PLHIV) who attained and maintained *undetectable* viral loads through HIV testing have significantly low risk of transmitting HIV to their partners, or people whom they have sexual relations with (US National Institute of Allergy and Infectious Diseases, 2019) - hence, *untransmittable*.
2. Promotion and provision of condoms and lubricants
3. Community and online outreach to increase HIV screening among key affected population

Description of Oral Pre-exposure Prophylaxis

Oral PrEP (Emtricitabine [FTC] 200 mg + Tenofovir Disoproxil Fumarate [TDF] 300 mg FDC) taken as a single pill once daily is used by people who are not infected with HIV (*seronegative*) to prevent being infected with HIV (WHO, 2021; Riddell, Amico, and Mayer, 2018). Components of oral PrEP (TDF/FTC) are both nucleoside analogue reverse transcriptase inhibitors (NRTIs). NRTIs typically prevent replication of HIV by inhibiting an HIV enzyme (*reverse transcriptase*) from converting the HIV RNA to DNA (US NIH Office of AIDS Research, n.d.; Blumenthal & Haubrich, 2013). When HIV replication is blocked, viral distribution and persistence is significantly decreased - thereby decreasing the risk of full-blown HIV infection. Oral PrEP is taken once a day. It can cause minor side effects (e.g. gastrointestinal disturbances) which typically fade after one month of using the drug (US CDC, n.d.).

Further, *emtricitabine + tenofovir disoproxil fumarate* 200 mg/300 mg FDC for oral PrEP to reduce the risk of sexually acquired HIV-infection is currently included in the 21st WHO Essential Medicine List published in 2019. Currently, this drug combination is not listed in the PNF and has a monitored-release Certificate of Product Registration (CPR) from the Philippine FDA. An MR-CPR is given to a drug that is newly introduced to the Philippines, regardless if the drug already has established safety data from international studies or not.

Following the WHO recommendation and its potential to prevent HIV in the Philippines, this evidence summary shall present the appraisal of evidence for the use of daily oral PrEP (emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg FDC) as an add-on to the currently mandated HIV prevention strategies to reduce the risk of acquiring HIV among at-risk populations. Current HIV preventive strategies in our review consist of (1) Advocacy of undetectable = untransmittable (U=U) messaging; (2) Promotion and provision of condoms and lubricants; and (3) Community and online outreach to increase HIV screening among key affected populations. This review shall serve as the evidentiary basis for the recommendation of the listing of Oral PrEP in the PNF (as all other drugs in combination are already listed in the PNF).

Policy Question

Should oral PrEP (emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg FDC) in tablet form be included in the Philippine National Formulary for individuals with substantial risk for HIV?

Research Questions

1. Clinical Effectiveness and Safety

- Among seronegative individuals who are at substantial risk of acquiring HIV,
    - what is the **efficacy and effectiveness** of adding oral PrEP (emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg FDC) to the combination prevention strategy as compared to combination prevention strategy alone in terms of maintaining HIV seronegative status, and improving adherence to the regimen?
    - what is the **safety** of adding oral PrEP (emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg FDC) to the combination prevention strategy compared to combination prevention strategy alone in terms of any adverse event, any stage 3 or 4 adverse event, and discontinuation of regimen?

2. Ethical, Legal, Social, and Health Systems Impact

- What are the **ethical, legal, social, and health system implications** of introducing oral PrEP (emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg FDC) as part of the existing preventive strategies to address HIV in the Philippines?

3. Economic/Budget Impact

- What is the cost-effectiveness of adding oral PrEP (emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg FDC) to the combination prevention strategy as compared to combination prevention strategy alone among seronegative individuals using societal perspective?
- What is the total medication cost for the expected number of seronegative individuals at substantial risk of acquiring HIV of adding oral PrEP (emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg FDC) to the combination prevention strategy as compared to combination prevention strategy alone for the first year of implementation?

- What is the total medication cost per user and for the expected number of seronegative individuals at substantial risk of acquiring HIV of adding oral PrEP (emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg FDC) to the combination prevention strategy as compared to combination prevention strategy alone for the first five years of implementation?

Responsiveness to Disease Magnitude, Severity, and Equity

Current prevalence/ severity of the disease

Global Burden of the disease

HIV continues to be a major global public health issue, having claimed 33 million lives so far. There were an estimated 38 million people living with HIV at the end of 2019 (HIV.GOV, 2020; UNAIDS fact sheet, 2020) Of these, 36.2 million were adults and 1.8 million were children; In 2019 alone, an estimated 1.7 million individuals acquired HIV (UN AIDS, fact sheet, 2020). While this is a significantly large number, it is a notable improvement, marking a 23% decline in HIV incidence since 2010 (HIV.GOV, 2020). In recent years, concerted international efforts to respond to HIV and steady increase in service coverage have improved the morbidity and mortality due to HIV. About 68% of adults and 53% of children living with HIV globally are receiving lifelong antiretroviral therapy, while 85% of pregnant and breastfeeding women living with HIV also receive ART which decreases the risk of HIV transmission to newborns (UNAIDS, 2020a). By the end of 2019, an estimated 81% of people living with HIV knew their status, with 59% achieving viral suppression. AIDS-related mortality also declined by 39% since 2010 (UNAIDS, 2020a).

HIV in the Philippines

In the Philippines, HIV affects less than 1% of the general population. An increase of 203% in HIV infections was observed from 2010 to 2018 (DM 2021-0017). The Philippines experienced the steepest rise in the number of cases in the Asia and Pacific region, and is considered as one of the eight countries accounting for 85% of new infections (DOH, 2020). The number of new HIV cases reported per day in the Philippines increased steadily from one case per day in 2008 to 21 cases per day in 2020. A total of 81,169 reported cases of HIV were reported in the Philippines between January 1984 to October 2020. In the month of October alone, there were a total of 735 confirmed HIV-positive individuals, 96% (704) of whom were male and 4% (31) were female. This incidence is in agreement with the current prevalence of HIV in the country—with 94% (76,216) comprising males and the majority (51%, 41,163) coming from the 25-34 years old age group at the time of diagnosis. Regions with the most number of reported cases were NCR with 30,622 cases (38%),

> CALABARZON with 12,467 (15%), Central Luzon with 8,005 (10%), Central Visayas with 6,827 (8%), and Davao Region with 4,477 (6%) (DOH, 2020)

From the data provided by the NASPCP, 6% of the MSMs and TWs are identified as having a substantial risk of acquiring HIV. The NASPCP based this on the number of people who do not know that condoms reduce risk of HIV transmission. Among these people, the projected number of oral PrEP users for 2022 is estimated at 10,000—75% of which will be covered by the Global Fund for HIV, while 25% is projected to be covered by DOH funds in 2022.

In accordance with Republic Act No. 11166, otherwise known as the "Philippine HIV and AIDS Policy Act, and its implementing rules and regulations (IRR), the Philippine government is tasked to initiate human rights-based and evidence-based policies, programs, and activities (PPAs) which decrease the effects of HIV among those who have it, and PPAs that prevent HIV transmission among at-risk populations. The law further provides protection for those who use PrEP and post-exposure prophylaxis (PEP) through the following:

> "*The presence of used or unused prophylactic shall not be used as basis to conduct raids or similar police operations in sites and venues of HIV prevention interventions*".

All HIV drugs in the Philippines are centrally procured through NASPCP and can only be accessed through HIV treatment hubs consisting of public and private facilities. If oral PrEP will not be included in the PNF:

- Subsidized HIV preventive services will be limited only to the non-pharmacologic options
- Accessing oral PrEP may incur out-of-pocket expenses once the donations from international partners cease

It can restrict both the general and at-risk populations from achieving better health outcomes.

Safety and Effectiveness

DESCRIPTION OF AVAILABLE EVIDENCE

The use of Oral PrEP has been supported by the WHO since 2013 and has been reiterated in the latest recommendation of the WHO published in July 2021. This most recent WHO guideline on Oral PrEP was supported by two systematic reviews: (1) Fonner et. al. in 2016 entitled *Oral pre-exposure prophylaxis (PrEP) for all populations;* and, (2) Chou et. al in 2019 entitled *Preexposure Prophylaxis for the Prevention of HIV Infection Evidence Report and Systematic Review for the US Preventive Services Task Force*. The former systematic review (Fonner et al, 2016) supported the earlier WHO recommendations on Oral PrEP in 2013. Meanwhile, the latter reference (Chou et al, 2019) is a more updated systematic review which essentially presents similar findings supporting the use of Oral Prep. This evidence summary shall focus on Chou et al (2019) since this is the most updated review which sought to: (1) evaluate the benefits of PrEP in individuals without preexisting HIV infection vs placebo or no PrEP on the prevention of HIV infection and quality of life; (2) evaluate the diagnostic accuracy of provider or patient risk assessment tools in identifying individuals at increased risk of HIV acquisition who are candidates for PrEP;- (3) identify the rates of adherence to PrEP in US primary care—applicable settings; (4) evaluate the association between adherence to PrEP and effectiveness for preventing HIV acquisition; and, (5) identify the harms of PrEP vs placebo or no PrEP when used for the prevention of HIV infection. This evidence summary shall focus on the review of objective numbers 1, 3, 4 and 5 which correspond to our research questions on the clinical efficacy and safety of Oral PrEP.

The review by Chou et al (2019) included a total of 29 studies corresponding to the five objectives of their review. Of the 29 included studies, 15 studies (9 Phase II/III RCTs and 6 real-world studies) are deemed to be relevant to our topic of interest (i.e., efficacy, effectiveness and safety of oral PrEP).

The population of these 15 studies includes uninfected adults and adolescents (13-18 years) at higher risk for acquiring HIV, specifically, people who inject drugs (PWID), MSM, women, men and high-risk heterosexual men and women were included in the studies. In total, the included studies have involved 12,145 participants across different populations and settings, with follow-ups ranging from 4 months to 4 years. Settings of the studies both include low-middle income countries and high income countries. The review included studies which evaluated oral PrEP containing tenofovir disoproxil fumarate (TDF) alone or in combination

with emtricitabine (FTC) as an add-on to other HIV preventive strategies such as HIV risk reduction and adherence counselling. On the other hand, comparators of the studies were either placebo (oral tablet but no drug component, in combination with other HIV preventive strategies) or no oral PrEP (i.e., other HIV preventive strategies alone). As for the outcomes measured in the review, the studies assessed for (1) HIV infection, which was classified as efficacy outcome in the research outcome, as well as (2) any adverse event, (3) adherence to PrEP, (4) mortality and harms, and (5) diagnostic test accuracy and discrimination. The authors did not provide an outcome definition for all outcomes explored.

The review performed meta-analysis using DerSimonian and Laird random effects model and the quality assessment of the individual studies. In their meta-analysis, the reviewers pooled the relative risks of HIV infection stratified by study drug (TDF alone and TDF+FTC) and in this evidence summary, we will be presenting the results only for the latter (i.e., TDF + FTC). The authors devised a quality assessment tool of pooled studies based on the following criteria: comprehensiveness of sources considered/search strategy used, standard appraisal of included studies, validity of conclusions, and recency and relevance. From the review of Chou et al, 2019, the HTAU assessment team performed a critical appraisal of their systematic review using the *A MeaSurement Tool to Assess Systematic Reviews (AMSTAR) 2 Tool*.

As for the additional Phase IV trial or real-world studies, there are two studies - one narrative review and one observational study - that are relevant to our research questions, which was based on the submission of the NASPCP and its international counterparts:

- Adams, 2019 - A narrative review on the real-world implementation studies of oral PrEP in the United States. The study summarized data on adherence and retention, adverse effects, and development of drug resistance. The review included 21 real world implementation studies conducted in the US since the FDA approval of TDF/FTC for PrEP in July 2012 were considered through July 2018. Of which, three have relevant outcomes for patient adherence and drug resistance. To note, this narrative review did not perform systematic search and selection and did not further appraise the included studies. Thus, results must be interpreted with caution.
- Koss, 2020 - An interim analysis of an ongoing observational study in Kenya and Uganda. The study assessed self-reported adherence up to 72 weeks, and concentrations of tenofovir in hair samples from individuals reporting HIV risk and adherence during follow-up. The study covered 3,489 participants at an elevated risk who initiated oral

PrEP (tenofovir disoproxil fumarate (300 mg) co-formulated with emtricitabine (200 mg) or lamivudine (150 mg) with enhanced PrEP counselling. However, results specific to each combination (i.e., TDF + 3TC and TDF + FTC) were not reported individually.

KEY FINDINGS FROM AVAILABLE EVIDENCE

Evidence from Phase II-III trials:

RCTs reviewed by Chou et al, 2019

In summary, in adults with increased risk of HIV infection, higher adherence with oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in combination with other HIV preventive strategies compared to placebo (oral tablet but no drug component, in combination with other HIV preventive strategies), was found to be significantly associated with reducing the risk for HIV infection.

As for the safety of oral PrEP, overall, there were no detected significant differences between oral PrEP and placebo in the majority of the safety outcomes analyzed except for safety outcomes related to *renal and gastrointestinal adverse events*.

Further, one study included in the systematic review of Chou et al (2019) found that oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) increases the risk of acquiring rectal chlamydia but not the risk of chlamydia at any site.

Efficacy of Oral PrEP

For the analysis on the efficacy of oral PrEP, the systematic review of Chou et al (2019) performed a meta-analysis of the efficacy outcome *reduction in the risk for HIV* from 8 RCTs which specifically administered our drug combination of interest for oral PrEP - TDF/FTC. Based on this specific meta-analysis, Chou et al (2019) found that oral PrEP (in combination with other HIV preventive strategies) reduces the risk of HIV infection vs placebo or no PrEP (RR: 0.44 [95% CI, 0.27-0.72]) with a substantial heterogeneity (I^2=74%) in the pooling of the 8 trials (n = 10,626).

Below is the meta-analysis of the 8 trials on the pooling of Risk Ratio for outcome HIV infection [Chou et al, 2019]:

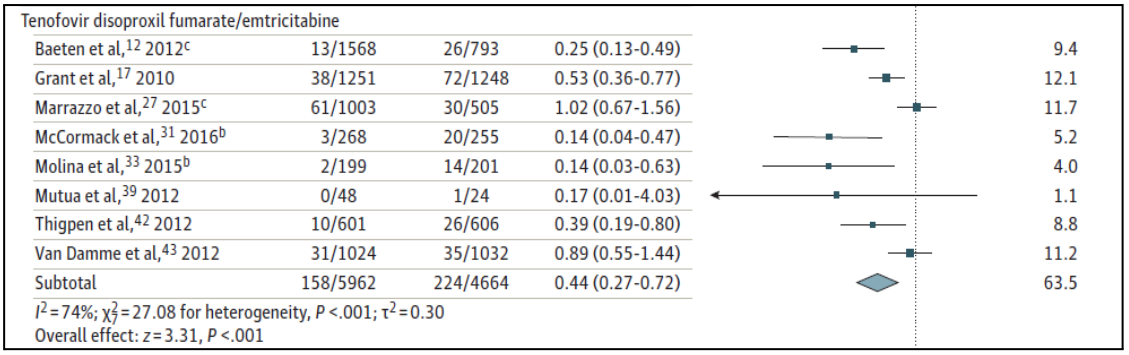

Figure 1. Meta-analysis of Oral PrEP (TDF/FTC) on HIV Infection

The systematic review of Chou et al (2019) also performed several subgroup analyses to assess the impact of (1) HIV risk category, (2) dosing schedule, (3) duration of follow-up, (4) study-reported support and (5) country setting in the efficacy of oral PrEP. However, these subgroup analyses included all studies on oral PrEP which were detected by Chou et al (2019), including those that administered TDF alone. The systematic review of Chou et al (2019) did not present any subgroup analyses that were specific for the trials that administered TDF/ FTC only. As such, these subgroup analyses were not included in this evidence summary.

In terms of the association of adherence level and efficacy of oral PrEP in preventing HIV acquisition, the systematic review by Chou et al (2019) performed a meta-analysis, although the analysis included trials for both TDF/FTC and TDF alone. Similar to other subgroup analyses mentioned above, the systematic review did not have specific results for TDF/FTC. Based on this analysis, Chou et al (2019) found a strong association between effectiveness (measured as hazard ratio for reducing the risk of HIV) of oral PrEP (TDF/FTC or TDF alone) and adherence to oral PrEP (measured as presence of detectable tenofovir on drug level testing, Medication Event Monitoring System (MEMS) data or pills count). Based on the stratification analysis, the effectiveness of oral PrEP between the adherence levels were significantly different (P < 0.001). The pooling of 6 trials which implemented oral PrEP at ≥70% level of adherence (n=7,328) showed a high reduction in the risk of HIV incidence (RR 0.27 [95% CI, 0.19-0.39]). The pooling of 3 trials with an adherence level of >40 to <70% (n=4,912) showed high reduction in the risk of HIV incidence (RR 0.51 [95% CI 0.38-0.70]). In contrast, the pooling of 2 trials (n=4,077) with a low adherence level of <=40% showed no

significant association with adherence and HIV incidence (RR 0.93 [95% CI 0.72-1.20]) .

Oral PrEP *(TDF/ FTC or TDF alone)* Adherence level	RR for HIV Infection	Number of studies included in the pooling
≤40%	**0.93** [95% CI 0.72-1.20]	2 studies
>40% to 70%	**0.51** [95% CI 0.38-0.70]	3 studies
≥70%	**0.27** [95% CI 0.19-0.39]	7 studies

Safety of Oral PrEP

As for the safety analysis of Chou et al (2019) there are a total of 9 trials which tested for statistical difference between oral PrEP (in combination with other HIV preventive strategies) vs placebo or no PrEP in terms of several safety outcomes.

Based on their analysis of safety outcomes, the results show that there was no significant difference between oral PrEP:

- *VS placebo* in terms of withdrawal due to adverse events (based on 4 studies), and herpes simplex virus infection (based on 3 studies)
- *VS placebo or no PrEP* in terms of serious adverse events (based on 9 studies), fracture (based on 6 studies), any bacterial transmitted infection (based on 2 studies), syphilis (based on 4 studies), gonorrhea (based on 5 studies), chlamydia (based on 5 studies) and hepatitis C virus infection (based on 2 studies)

Meanwhile, there were two safety outcomes where significant difference was detected by Chou et al (2019):

- *Renal adverse events* - the oral PrEP arm had a total of 174/6,037 (2.9%) while the placebo or no PrEP arm had 98/4701 (2.08%). Results show that oral PrEP was associated with increased risk of renal adverse events compared with placebo or no PrEP (RR, 1.54 [95% CI, 1.21-1.96]), based on the pooling of 9 of studies. The level of heterogeneity for the pooling of renal eventsis 0% denoting low heterogeneity. It was noted by Chou et al (2019) that renal abnormalities were primarily 1 or more grade-1 elevation of serum creatinine

level which is alleviated by PrEP cessation or with ongoing PrEP and that the presence of serious renal events was rare.

- *Gastrointestinal adverse events* - the oral PrEP arm had a total of 246/6,038 (4.07%) while the placebo or no PrEP arm had 105/4,702 (2.23%). There was an increased risk in the oral PrEP compared with placebo or no PrEP (9 trials; [RR, 1.84 [95% CI, 1.26-2.70]). The level of heterogeneity for this outcome in this pooling is 49% which shows that results should be interpreted with caution. It was noted by Chou et al (2019) that the presence of gastrointestinal events was rare.

Table 1 below shows the association of adverse events and sexually transmitted infections with oral PrEP.

Table 1. ***Key Findings from Chou et al, 2019 on the Adverse Events and Sexually Transmitted Infections in Randomized Clinical Trials of oral PrEP (FTC/TDF) vs Placebo/No PrEP***

Outcome	No. of Trials	RR (95% CI)	I^2, %
Outcomes with no statistical or clinical significant difference			
Oral PrEP vs Placebo			
Withdrawal due to adverse events	4	1.27 (1.00-1.59)	0
Herpes simplex virus infection	3	0.86 (0.62-1.18)	40
Oral PrEP vs Placebo or no Oral PrEP			
Serious Adverse Events*	9	1.02 (0.81-1.30)	46
Fracture	6	1.06 (0.66-1.72)	0
Any bacterial sexually transmitted infection	2	1.07 (0.80-1.44)	58
Syphilis	4	1.07 (0.98-1.18)	0
Gonorrhea	5	1.15 (0.97-1.37)	2
Chlamydia	5	1.07 (0.94-1.22)	0
Hepatitis C virus infection	2	0.73 (0.25-2.10)	0
Outcomes with significant difference			
Oral PrEP vs Placebo or no Oral PrEP			
Renal adverse events	9	1.54 (1.21-1.96)	0

Gastrointestinal adverse events	9	1.84 (1.26-2.70)	49

**WHO definition: Any untoward medical occurrence that at any dose results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization and results in persistent of significant disability or incapacity.*

Quality of studies reviewed by Chou et al, 2019

Among the 9 included studies for our research question of interest, 6 were rated with "Good" quality. Meanwhile, 3 studies were with "Fair" quality citing lack of blinding for 2 studies and unclear blinding for 1 study. The overall quality of all 9 studies was "Good".

Critical Appraisal of Chou et al, 2019

As for our appraisal for Chou et al (2019), the overall rating by the assessment team yielded an interpretation of critically low quality of evidence. Critical flaws observed included: (1) no mention of justification for any deviations from the protocol, review not registered prior, (2) no mention if searched trial/study registries included/consulted content experts in the field, (3) no list of excluded studies that are potentially relevant, (4) no mention of allocation sequence and selection of the reported result from among multiple measurements or analyses of a specified outcome and (5) no discussion was found for the potential impact of bias in the quality of studies. The detailed appraisal rating can be found on Appendix 1. Despite the evidence having a rating of critically low quality of evidence based on AMSTAR II tool, the joint Subcommittee on Drugs and Preventive and Promotive Health deems that the review is still useful in assessing oral PrEP.

Evidence from Phase IV trials/Real-world studies

Real-world studies reviewed by Chou et al, 2019

In summary, six observational studies were included in this review. However, none of which measured the real-world clinical effectiveness outcomes for oral PrEP. Further, the studies included did not have a comparator arm. In addition, adherence was the primary outcome of the review rather than real world effectiveness. The results of the six studies showed that the adherence to oral PrEP in combination with other HIV

preventive strategies decreases in the long run. Hosek et al, 2017A and Hosek et al, 2017B included the safety profile of oral PrEP in their study. These studies indicated that unintentional grade 3 weight loss, nausea, and headache may be attributable to oral PrEP. Table 2 shows the characteristics of the study.

Table 2. ***Study characteristics of real-world studies reviewed by Chou et al, 2019***

	Chan et al 2016 [Prospective Cohort]	**Project PrEPare / ATN 113, Hosek et al, 2017A [Treatment Series]**	**Project PrEPare / ATN 110 Hosek et al, 2017B [Prospective Cohort]**	**PATH-PrEP Landovitz et al, 2017** [Treatment Series]	**Montgomery et al, 2016** [Treatment Series]	**U.S. PrEP Demonstration Project Liu et al, 2016** [Treatment Series]
P	N= 267 MSM (89%), MSF (5.2%), FSM (6.7%)	N=72 MSM aged 15-17 years	N=200 MSM Mean age: 20	N=301 MSM and transgender women Median age: 36	N=50 MSM adult Mean age: 34	N=557 MSM and transgender women Mean age: 35
I	Oral PrEP TDF/FTC	Oral PrEP TDF/FTC in conjunction with behavioral intervention	Oral PrEP TDF/FTC with behavioral counseling	Oral PrEP TDF/FTC with PrEP-based HIV prevention package	Oral PrEP TDF/FTC	Oral PrEP with HIV testing, brief client-centered counseling, and clinical monitoring
C	None	None	None	None	None	None
O	Adherence and retention in PrEP care at three and six months	Safety, tolerability, and acceptability of TDF/FTC and patterns of use, rates of adherence, and patterns of sexual risk behavior	Adherence and safety	Adherence to PrEP	Self-reported drug adherence as well as drug concentrations in dried blood spots (DBS) oral PrEP	Adherence to PrEP based on concentrations of tenofovir diphosphate in dried blood spot samples

Adherence to Oral PrEP in US Primary Care-applicable Setting

The 6 studies were primarily about MSMs in the US. The study of Landovitz et al. 2017, Montgomery et al. 2016 and Liu et al. 2016 (Mean age: 34-36 years, N=908) found that at ≥4 doses/week, adherence to PrEP based on a tenofovir diphosphate level of 700 fmol/punch or greater than dried blood sampling, adherence to oral PrEP was 66%-90%. Meanwhile, Hosek et al. 2017A (Mean age: 16-20 years, N=72) found that adherence to oral PrEP at 12 weeks was at 50%, while 22%-34% at 48 weeks. Further, Hosek et al. 2017B (Mean age: 20, N=200) found that adherence to oral PreP at week 12 was 53% and went down to 34% at week 48.

Further, adherence to oral PrEP based on dried blood spot (DBS) sampling levels consistent with ≥4 doses per week ranged from 22% to 86%. Adherence to oral PrEP at week 4 ranged from 54% to 85% while adherence at week 48 ranged from 22 to 80%. Self-reported adherence ranged from 56% to 92% in the study of Chan et a. 2016. However, the cited limitations of the study as noted by Chou et al (2019) were high attrition and variability in methods for measuring adherence, as well as only studies in the US Primary Care Settings were included. Table 3 shows the adherence outcomes reported of the studies in the review.

Safety of Oral PrEP

The study by Hosek et al., 2017A noted that TDF/FTC was well-tolerated by the participants. No significant laboratory abnormalities were observed, and most adverse events present were not related to the treatment. However, unintentional grade 3 weight loss was experienced by one patient, which the investigators presume to be attributed to the treatment.

In Hosek et al., 2017B, three grade 3 adverse events (nausea, weight loss, and headache) among three participants were observed which may be attributed to TDF/FTC treatment. Resolution of these adverse events was observed upon discontinuation of treatment. The study further pointed out the occurrence of a single renal event (grade 1 elevation of serum creatinine) which was noted at the last study visit then resolved by a subsequent safety follow-up visit. The study does not specify if this renal event could be attributed to the study treatment. Some of the 22 participants discontinued treatment due to self-reported side effects, one of them being gastrointestinal discomfort. Twenty-one grade 3 or

higher adverse events occurred among 15 participants. These were deemed to be irrelevant to treatment.

Quality of the observational studies covered by Chou et al, 2019

All 6 studies were rated “Fair” quality by Chou et al. The 6 studies were noted to have performed the following: have used accurate methods for ascertaining exposures and potential confounders; have pre-specified and defined, and ascertained outcomes using accurate methods; and, have reported attrition (with 4 of 6 studies reporting high attrition).

However, 4 of 6 studies had unclear attempts to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample. Meanwhile, 5 of 6 studies did not blind outcome assessors and/or data analysts to the exposure being studied.

Adherence

Table 3. ***Summary of Adherence Outcomes from the Observational Studies of the Review of Chou et al, 2019***

Study	Population	Adherence based on Drug levels	Self-reported Adherence	Other methods of assessing adherence
Chan, 2016	N= 267 MSM (89%), MSF (5.2%), FSM (6.7%)	Not reported	4 or more pills in last week: 92% (106/115) at 3 months, 92% (73/79) at 6 months 100% adherence in the last week: 72% (83/115) at 3 months, 79% (64/81) at 6 months 100% adherence in last month: 49% (56/115) at 3 months, 56% (44/79) at 6 months	Not reported
Hosek, 2017A	N=72 MSM	DBS with TFV-DP level ≥700 fmol/punch Week 4: 54% Week 8: 47% Week 12: 49% Week 24: 28% Week 36: 17% Week 48: 22% DBS with TFV-DP level ≥350 fmol/punch Week 4: 69% Week 8: 66% Week 12: 59% Week 24: 36% Week 36: 28% Week 48: 26%	Not reported	Not reported
Hosek, 2017B	N=200 MSM	DBS samples with TFV-DP level ≥700 fmol/punch Week 4: 56% Week 8: 58% Week 12: 53% Week 24: 47% Week 36: 41% Week 48: 34%	Not reported	Not reported

		Any TFV-DP level detected: 92% at week 4, 69% at week 48		
Landovitz, 2017	N=301 MSM and TW	DBS samples with TFV-DP ≥700 fmol/punch: Week 4: 83.1% Week 12: 83.4% Week 24: 75.7% Week 36: 71.6% Week 48: 65.5%	Not reported	Not reported
Liu, 2016	N=557 MSM (98%) and TW	DBS samples with TFV-DP level ≥700 fmol/punch Week 4: 86% Week 12: 85% Week 24: 82% Week 36: 85% Week 48: 80% ≥2 DBS samples meeting threshold: 62.5% (170/272) TFV-DP level ≥350 fmol/punch, ≥2 DBS samples meeting threshold: 97% (264/272)	Adherence self-rated "very good" or "excellent" at 87% (1,959/2,242) of visits	Pill count: 81.6% Medication ratio (number of dispensed pills/the number of days between visits): 85.9%
Montgomery, 2016	N=50 MSM (95%)	DBS samples with TFV-DP level ≥700 fmol/punch at mean 4.4 months: 90% (19/21) TFV-DP level ≥350 fmol/punch: 95% (20/21)	Mean proportion of doses taken in the last 7 days, at 3 months: 89% (6.2/7) Mean proportion of doses taken in the last 30 days, at 6 months: 89% (26.8/30)	Not reported

Observational studies covered by ADAMS ET AL, 2019

The narrative review of Adams et al. (2019) included three observational studies (Grant et al, 2014; Hosek et al, 2017B; Liu et al, 2016). Among the cohort studies, one (Grant et al, 2014) compared HIV infections of those who took PrEP and who chose not to take PrEP, while the other study (Liu et al, 2016) did not follow up on those who did not initiate PrEP. All of the studies included MSM as participants while two (Grant et al, 2014; Liu et al, 2016) of the studies also included TW. Outcomes considered in the review were HIV incidence, adherence, drug resistance, and adverse events. In summary, the real world implementation data from this narrative review demonstrated a decreasing number of new occurrences of HIV infection with increasing adherence to oral PrEP. Meanwhile, safety results show that grade 1 adverse events are the most common among oral PrEP users. To note, this narrative review did not perform systematic search and selection and did not further appraise the included studies; thus, results must be interpreted with caution.

Effectiveness of Oral PrEP

HIV incidence among those who used PrEP was 1.8 infections per 100 person-years compared to 2.6 infections per 100 person-years among those who did not take PrEP (Grant et al, 2014). In comparison, 3.3 infections per 100 person-years were recorded among those who used PrEP in the study by Hosek et al (2017B). In terms of drug resistance, there was a seroconversion with M184V mutation in one study. For the other two studies (Hosek et al, 2017A; Liu et al, 2016), no resistance was detected. In one study (Grant et al, 2014) where there were seroconversions, their tenofovir diphosphate (TFV-DP) concentrations were correlated with taking <2 doses per week. Table 4 shows the summary of effectiveness outcomes of the included studies.

Adherence to Oral PrEP

Adherence to oral PrEP ranged from 33% to 63%. Notably, the study with the highest adherence had the lowest HIV incidence (0.4%). Moreover, 90% still had detectable drug concentrations at 12 weeks while 69% at 48 weeks in the observational study of Hosek (2017B). Table 4 also shows the summary of adherence outcomes of the included studies.

Table 4. ***Summary of Effectiveness and Adherence Outcomes from the Review of***

Adams et al, 2019

Study	Population	HIV Incidence	Drug resistance	Adherence ≥ 4 doses/ week by drug concentrations
Grant (2014)	n=1,225 MSM, TW	28 HIV Infections (7 had discontinued PrEP) 1.8/100 py among participants who received PrEP vs. 2.6/100 py among participants without PrEP	1 seroconversion with M184V mutation	33% adherence; HIV incidence: 0.0/100 py* with ≥4 doses/week vs. 4.7/100 py* with no drug in DBS (p<0.0001)
Hosek (2017B)	n=200 MSM	4 HIV infections 3.3/100 py among participants who received PrEP	No resistance detected; no detectable TFV-DP in the 4 patients who seroconverted	34% at 48 weeks; 90% had detectable drug concentrations at 12 weeks and 69% had detectable at 48 weeks
Liu (2016)	n=557 MSM, TW	2 HIV infections Incidence 0.4% (95% CI 0.1 to 1.5) among participants who received PrEP	No resistance detected; both seroconversions had TFV-DP concentrations correlated to <2 doses/week	63% adherence; 2.9% had concentrations consistently correlated to <2 doses/week

py - person years; HR - hazard ratio; DBS- dried blood spots

Safety of Oral PrEP

For the safety outcomes (Table 5), the most common adverse events among the participants who took Oral PrEP were grade 1 increases in serum creatinine which were evident across the three studies. An instance of grade 2 increases in serum creatinine was also noted in two separate studies. Grade 3 events (e.g. nausea, weight loss, headache) and significant decrease in bone mineral density were noted in one study. The review concluded that adverse events from TDF/FTC when taken for oral PrEP in HIV-negative populations appear to be similar to those seen in the HIV-infected population when taken for treatment. No comparison was

made between those with and without PrEP in the cohort study (Grant et al, 2014) that included participants who did not take PrEP.

Table 5. ***Summary of Safety Outcomes from the Review of Adams et al, 2019***

Study	Population	Adverse Effects
Grant (2014)	MSM, TW (n=1,225)	22 grade 1 and 1 grade 2 increases in serum creatinine
Hosek (2017B)	MSM, 18-22 years (n=200)	3 grade 3 events (nausea, weight loss, headache) 1 grade 1 increase in serum creatinine Significant decreases in bone mineral density Z-scores in the hip (−0.4%; p<0.001) and whole body (−0.6%; p<0.001)
Liu (2016)	MSM, TW (n=557)	22 grade 1 and 1 grade 2 increases in serum creatinine

KOSS ET AL, 2020

Koss et al (2020) presented interim results of an ongoing observational study of PrEP recipients. Koss et al (2020) assessed self-reported adherence up to 72 weeks, and concentrations of tenofovir in hair samples from individuals reporting HIV risk and adherence during follow-up. The study covered 3,489 participants at an elevated risk who initiated oral PrEP (tenofovir disoproxil fumarate (300 mg) co-formulated with emtricitabine (200 mg) or lamivudine (150 mg) with enhanced PrEP counselling. However, there was no disaggregation in the presentation of results and type of regimen received by the participants. Furthermore, the study did not have a comparator or a placebo arm.

Adherence to Oral PrEP

For the effectiveness outcomes, a multivariable mixed-effects logistic regression by Koss et al (2020) showed different factors that may be associated with self-reported adherence to oral PrEP in the interim results of their study. The study showed that the youngest age group was negatively associated with self-reported adherence. Being divorced, separated, or widowed, and being in a serodiscordant relationship was positively associated with adherence to oral PrEP. Remarkably, self-assessed current HIV risk had the highest odds with adherence.

Table 6. ***Factors associated with Self-reported Adherence***

Variable	Adjusted OR	Interpretation
Age Group		
15-24	0.59 (0.40–0.86)	Negatively associated to Oral PrEP adherence
25-34	0.86 (0.63–1.17)	Not significant
35-44	Reference	
>=44	0.98 (0.68-1.41)	Not significant
Marital Status		
Not married	Reference	
Married (monogamous)	1.23 (0.81–1.88)	Not significant
Married (polygamous)	1.41 (0.87–2.28)	Not significant
Divorced/Separated/ Widowed	2.10 (1.12–3.95)	Positively associated to Oral PrEP adherence
Serodifferent partnership		
No/unknown	Reference	
Yes	1.64 (1.22–2.19)	Positively associated to Oral PrEP adherence
Self-assessed current HIV Risk		
No	Reference	
Yes	12.36 (9.39–16.28)	Positively associated to Oral PrEP adherence

Using mixed-effects logistic regression also adjusted for sex, occupation, educational attainment, alcohol use, and migration/mobility (variables not significant)

Safety of Oral PrEP

For the safety outcomes, the most common adverse events in the interim report were spontaneous abortion and abdominal pain. Any grade 3 or 4 adverse event rate was recorded below 1%. Five grade 3 adverse events were possibly related to oral PrEP. Grade 3 creatinine elevation occurred to 1 user can be linked to the use of the TDF/FTC since cessation of its use lead to the return to its baseline level. Seven deaths were noted with no direct link to the use of the drug.

Table 7. ***Summary of Safety Outcomes from Koss et al, 2020***

Outcome	N (%)	Interpretation
Any grade 3 or 4 adverse event	28 (0.8%)	Grade 4 events recorded were anemia (2), pre-eclampsia (1), ruptured ectopic pregnancy (1), soft tissue injury (1), and suicide attempt by poisoning (1). Most common grade <=3 events were abdominal pain (4) and spontaneous abortion (5).
Grade 3 creatinine elevation	1 (0.03%)	One grade 3 creatinine elevation occurred in a 71-year-old man who was treated in hospital for urinary retention and hydronephrosis. Creatinine returned to baseline following relief of urinary obstruction and cessation of the study drug.
Grade 4 creatinine elevation	0	No grade 4 creatinine elevation was recorded.
Grade 3 adverse event possibly related to the study drug	5 (0.1%)	Five adverse events (all grade 3) were assessed as being possibly related to the study drug.
Grade 4 adverse event possibly related to the study drug	0	No grade 4 adverse event was linked to the study drug.
Any serious adverse event	29 (0.8%)	29 of 3489 participants who initiated PrEP had serious adverse events, including seven deaths.
Death	7 (0.2%)	Causes of death were either of the following: complications of alcohol use, diabetic ketoacidosis, drowning, injuries following motor vehicle accident, murder, or tuberculosis. One unknown cause of death was also noted

Ethical, Legal, Social, and Health Systems Impact

This section shall provide evidence on the ethical, legal, social and health systems implications of introducing Oral PrEP in combination with other preventive strategies on HIV. Evidence presented here was sourced from (1) literature review; and (2) a series of focus group discussions.

EVIDENCE FROM PUBLISHED STUDIES

Review of literature: ETHICAL AND SOCIAL IMPLICATIONS

Description of available evidence

Evidence was scoped from available studies (n=55) given by the NASPCP on trials and other relevant studies on oral PrEP. Out of 55, only four studies were included. The rest of the excluded studies were either not about emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg FDC or not related to ethical, social, legal, and/or health systems impact of oral PrEP. Of the included studies, three were international studies (Molina et al, 2015; Roux et al, 2018; Ciaccio et al, 2021), and one was conducted in the Philippines (PrEPPY Technical Report, 2019). These studies included outcomes that explored the social impact of using oral PrEP (emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg), whether on-demand or daily, as part of preventive strategies in addressing HIV. In total, there are 4 studies that will be elaborated in this subsection.

Molina et al (2015) performed a clinical trial that analyzes the efficacy of on-demand oral PrEP against contracting the HIV virus among MSMs and TWs. *ANRS-IPERGAY trial* was originally a phase III multi-centre, comparative, double-blind, randomized trial which evaluated the seroconversion of HIV-negative MSMs as they use of on-demand oral PrEP (tenofovir disoproxil fumarate and emtricitabine) compared to placebo, in 2012. The participants respondents (n=400) were given a loading dose of two pills of oral PrEP, each including 300 mg of TDF and 200 mg of FTC in a fixed-dose combination. This was then followed by a third pill 24 hours after the first drug intake and a fourth pill 24 hours later. Study visits were scheduled 4 and 8 weeks after enrollment and every 8 weeks thereafter. Each visit included drug dispensation with enough pills to cover the daily use of TDF-FTC or placebo between visits, pill count and adherence counseling, serum testing for HIV-1 and HIV-2, and biochemical analyses.

Prior to the visits, the respondents were asked to accomplish a computer-assisted survey questionnaire to collect data on sociodemographic characteristics, alcohol and recreational drug consumption, adherence to oral PrEP during the most recent sexual intercourse, and self-reported sexual behavior. The two other international studies (Roux et al, 2018; Ciaccio et al, 2021) analyzed outcomes from the trial conducted by Molina et al (2015) - i..e, the ANRS-IPERGAY trial. In November 2014, all participants still being followed up (n = 336) were invited to voluntarily enroll in the open-label extension (OLE) phase study of the ANRS-IPERGAY trial, which immediately followed the discontinuation of the placebo-controlled randomized phase. Upon "proof of on-demand PrEP effectiveness", all participants still being followed up (n = 336) were invited to voluntarily enroll in the OLE study of the ANRS-IPERGAY trial, which immediately followed the discontinuation of the placebo-controlled randomized phase. The results of the OLE phase of the trial was reported by Roux et al, 2018, specifically to investigate the correlation among the following variables: the correct use of PrEP, chemsex/slamming engagement, and sexual practices. In this context, *chemsex* refers to the use of psychoactive substances (i.e., GHB/GBL and synthetic cathinones) during any sexual activity. Meanwhile, *slamming* is the act of injecting intravenous psychoactive drugs prior to engaging in sex. Using a generalized estimating equation (GEE) logistic regression, association among chemsex practice, correct PrEP use, and sexual practices were determined by the authors.

Meanwhile, Ciaccio et al (2021) conducted a comparative analysis on the changes in sexual behavior and relationships among respondents between the double-blind clinical trial phase of the study (DBP) and the OLE phase. It studied both protective and risky behaviors among 332 participants enrolled in the DBP and OLE phases. The mean age of respondents is 35.8 years.The study characteristics of the original trial and the OLE phase of the study are described in Table 8.

For the local study, Ditangco et al (2019), a 24-month pilot project of community-based peer-driven HIV PrEP in the Philippines, was conducted in 2018 which aimed to encourage wider implementation of oral PrEP use among MSM and TW. The project also aims to evaluate social factors such as feasibility, acceptability, adherence, and behavioral changes while documenting HIV prevalence and incidence at the community level. The conduct of the project was done at two (2) Love Yourself (LYS) Foundation operated clinics located in Metro Manila. LYS is a community-based organization for MSM/TW supported by the Department of Health of the Philippines.

By the end of the enrollment period on December 28, 2017, around 250 clients had been successfully enrolled.

The studies used oral PrEP in combination with non-pharmacologic interventions, and not alone. The HTAC recognizes that these interventions, when given with oral PrEP, may serve as confounders to the results of the study.

Table 8. Summary of characteristics of Included studies

	ANRS-IPERGAY Trial	**ANRS-IPERGAY Open Label Extension**	**PrEPPY Technical Report (2019)**
Publication of results	Molina et al, 2015	Roux et al, 2018 (as cross sectional analysis) Ciaccio et al, 2021 (as comparative analysis compared to the trial results)	Ditangco et al, 2019 (as Project Technical Report)
Dates	Study Start Date: January 2012 Actual Study Completion Date: May 11, 2017	Study Start Date: November 4, 2014 Actual Study Completion Date: June 30, 2016	Project Start Date: July 2017 Project Completion Date: December 2017 **Post-project extension was performed to provide oral PrEP to participants for 12 months.*
Study Design	Phase III, multi-centre, comparative, double-blind, randomized trial	Roux et al, 2018: Open label study, cross sectional analysis Ciaccio et al, 2021: Open label study, comparative analysis between OLE and DBP study	*Project-based Technical Report*
P	N = 400 MSM France and Canada	Roux et al, 2018 analysis: N=331 Participants with available data about use of psychoactive substances who were part of the OLE of the ANS-IPERGAY Trial Ciaccio et al, 2021 analysis: N=332	● HIV-negative males or transgender women having sex with other men ● Must have sexual and/or drug use-related risk behaviors for HIV (*Specific parameters on HIV risk in the protocol were not defined*). N = 158 Country Setting: Philippines

		MSM taking sexual activity-based PrEP	
I	tenofovir disoproxil and emtricitabine *2 tablets of truvada within 24 hours before first sexual relations, then 1 tablet of Truvada during the period of sexual activity including the last sexual intercourse, finally, a last dose of 1 tablet of Truvada approximately 24 hours later*	Oral Pre-Exposure Prophylaxis (PrEP) - tenofovir disoproxil and emtricitabine	Oral PrEP (TDF-FTC) one tablet taken once daily
C	Placebo	Roux et al, 2018: None Ciaccio et al, 2021: PrEP arm of the DBP	No comparator
O	Primary: Contamination with HIV-1 or -2 Secondary: ● Evolution of sexual behavior and potential at-risk behavior ● Incidence of clinical and biological adverse events ● Treatment adherence ● Incidence of hepatitis B ● Incidence of other sexually transmitted diseases ● Frequency of HIV resistance to antiretrovirals in HIV infected subjects ● Emtricitabine and tenofovir concentrations in plasma, saliva and rectal samples ● Costs evaluation	Roux et al, 2018: Correct PrEP use during the most recent sexual encounter Ciaccio et al, 2021: Sexual behaviors of participants in the DBP and OLE phases	● Sexual and drug use-related risk behavior change over time ● Breakthrough HIV and sexually-transmitted infections ● Self-reported oral PrEP adherence
Analyses	Association of "on demand" antiretroviral pre-exposure prophylaxis using Truvada (versus placebo) vs. overall prevention (counselling, condoms, sexually transmitted diseases (STD) screening, hepatitis B virus (HBV) and hepatitis	Roux et al, 2018: The association of Chemsex with correct PrEP use was computed using a generalized estimating equation approach Ciaccio et al, 2021: Chi-square tests for dichotomous	No specified form of analysis (because this is a ***project report***) ● **Indicator 1**: PrEP Uptake (Percentage of eligible people who received antiretroviral

	A virus (HAV) vaccinations and post-exposure treatment of HIV infection) in men who have sex with men (MSM), exposed to the risk of HIV infection.	& categorical outcomes; T-Test for continuous outcomes	PrEP at least once in the past 12 months) • **Indicator 2**: Continuation of PrEP. Percentage of PrEP users continuing for three months after initiating PrEP • **Indicator 3**: PrEP associated toxicity. Percentage of people who received PrEP but were discontinued due to toxicity during the past 12 months • **Indicator 4**: PrEP related HIV seropositivity. The percentage of people who tested HIV positive after receiving PrEP.

Key findings from the reviewed studies

Sexual Practice and Behavior

Results from Molina et al, 2015 indicated no change in sexual practices throughout the study period. No significant between-group differences were observed in the total number of sexual intercourse episodes 4 weeks before visits (P=0.07), proportion of episodes of receptive anal intercourse without condoms (P=0.40), and proportion of episodes of anal sex without condoms during most recent sexual intercourse (P=0.90). Similar proportions were also seen among participants with new sexually-transmitted infections in the throat, anus, and urinary tract (41% in the TDF-FTC group vs. 33% in the placebo group, P=0.10). However, it is important to note that in the ANRS IPERGAY trial, participants were also given other non-pharmacologic HIV-preventive interventions in conjunction with their scheduled visits for drug dispensation. This includes peer counselling, free condoms and gel, and diagnosis and treatment of sexually transmitted infection, which may also influence sexual practice and behavior.

Roux et al, (2018) studied sexual practices related to chemsex and the use of oral PrEP among MSMs and TW. About 331 respondents from France and Canada were asked to fill in questionnaires related to oral PrEP use annually and biennially. Among them, 30% reported engaging at least once in chemsex at baseline. In terms of socio-demographic characteristics, chemsexers did not differ significantly when compared with non-chemsexers. The authors posited that performance of chemsex/slamming was associated with correct and appropriate use of oral PrEP, even after adjustment for other potential correlates (OR = 2.24 [1.37 to 3.66] at 95% confidence interval). Chemsex/slamming was associated with increased recurrence of receptive anal sex, increased HIV exposure, and "*hardcore sexual practices*". However, respondents who used oral PrEP and engaged in chemsex have a significantly higher perception of HIV transmission as compared to those who did not engage in chemsex.

In the analysis by Ciaccio et al, (2021), based on the GEE model estimates, the proportion of individuals who engaged in condomless anal sex (CAS) increased significantly (32% per year), but only during the OLE phase. It was observed that both protective and risky sexual behaviors increased while the respondents were on oral PrEP. Aside from HIV, CAS can increase the risk of transmission of other sexually transmitted infections.

In a pilot project for oral PrEP in the Philippines (Ditangco et al, 2019), the investigators observed that among at-risk HIV-negative MSM and TW, more than 90% of men reported anal sex with their steady and casual partners at baseline. However, the project reported a decline in the percentage of men practicing anal sex with casual sex partners from 93.3% at baseline to 83.1% after the observation period (ie., 12 months) (p=0.001), and of selling sex from 16.0% at baseline to 8.9% (p<0.01) after 6 months. Furthermore, it is noted that the project was implemented in two (2) LoveYourself-operated clinics in Metro Manila, which involves screening, counselling, and enrollment. These adjunct interventions could have affected the behavioral results of the study.

Sexual Relationships

Molina et al, 2015 observed a slight but significant decrease in the number of sexual partners within the past two months was observed in the placebo group (7.5) as compared to the TDF-FTC group (8) (P=0.001).

Roux et al, (2018) reported that chemsex/slamming was associated with increased likelihood of having casual sexual partners (P ≤ 0.001).

Meanwhile, Ciaccio et al, (2021) showed a significant decrease in the number of sexual partners (decrease of "0.37 partners" [CI at 95%, − 0.37 [− 0.70 to − 0.04], p = 0.03] in the OLE during the previous two months) and in the number of sexual relations (decrease of "0.25 sexual relations" [CI at 95%, − 0.25 [− 0.49 to 0.00], p = 0.04]) in the OLE in the previous four weeks) between the DBP and OLE phases. Specifically for sexual relations, the proportion of sexual relations with an unknown casual partner was 25% lower on average in the OLE phase as compared to the DBP phase.

Project PrEPPY (2019) observed that the participants had a mean number of 13.5 sexual partners at baseline and increased significantly to 16.7 at the end of the first year (p<0.05 at 95% CI). Moreover, the number of steady sexual partners increased from a mean of 2.4 partners at baseline, to 3.0 after one year (p<0.02 at 95% CI). Lastly, it was noted that the recorded number of casual partners did not increase over time.

Substance Use

In Roux et al, 2018, of all questionnaires distributed and accomplished, 16% reported engaging in chemsex while 30% declared engaging at least once in chemsex after 2

months. Furthermore, performance of chemsex/slamming was associated with correct and appropriate use of oral PrEP, even after adjustment for other potential correlates (OR = 2.24 [1.37 to 3.66] at 95% confidence interval).

In terms of substance use in addition to oral PrEP, Ciaccio et al, (2021) reported the following outcomes:

(1) Proportion of respondents who engaged in sex and in the use of recreational drugs (44.6% in DBP vs. 55.4% in OLE, p=0.3) while on oral PrEP did not have any significant change;
(2) Proportion of respondents who engaged in alcohol consumption (51.6% in DBP vs. 48.4% in OLE, p<0.001) significantly decreased while on oral PrEP; and
(3) Upon the creation of generalized estimating equation (GEE) models, it was observed that alcohol consumption while having sexual relations significantly decreased while on oral PrEP.

Ditangco et al (2019) reported that binge drinking, defined as the intake of not less than seven alcoholic beverages in one sitting, among participants was noted to be consistent from baseline to end of year 1. However, drug (e.g. mind-altering substance) use was reported to increase from 29.6% at baseline to 36.1% after 6 months (p<0.02 at 95% CI). Consequently, the percentage of participants who believed that alcohol and drug intake would not negatively affect their PrEP use rose from 82.4% at baseline to 91.1% after six months (p<0.02 at 95% CI).

PrEP in combination with other HIV Strategies

For this outcome, Ciaccio et al, (2021) reported a significant increase in the percentage of respondents who engaged in sex and used 'PrEP only' (39.9% at baseline vs. 60.1% after the 18 months, p<0.005) and with 'both PrEP and condom use' (48.3% in the DBP vs. 51.7% in the OLE, p<0.001). Meanwhile, Roux et al, (2018) did not report results of PrEP in combination with other HIV strategies.

In the Philippines, Ditangco et al, (2019) observed that consistent condom use for the past 6 months while doing anal sex with steady partners decreased from 26.2% to 10.7% (p<0.001 at 95% CI) after year 1. Similarly, condom use during the latest sexual relations while being drunk or high decreased from 38.1% at baseline to 19.7% after 6 months (p<0.001 at 95% CI).

Review of Policies: LEGAL IMPLICATIONS

We reviewed several policies relevant to HIV and oral PrEP and classified them into three: (1) policies which are enabling the use or access to oral PrEP; (2) policies where potential barriers or challenges on accessing oral PrEP may arise; and, (3) policies relevant to other HIV services which may indirectly impact or relate to the access of oral PrEP.

Policy Enablers for Oral PrEP

Existing Policies Enabling Service Delivery

Republic Acts

The mandates below have been promulgated with the goal of enabling the implementation of HIV-related preventive and promotive services in the country, such as oral PrEP. The Philippine HIV and AIDS Policy Act of 2018.

RA 11166 or "The Philippine HIV and AIDS Policy Act of 2018" aims to:

(1) establish policies and programs focused on preventing the spread of HIV while being able to deliver treatment, care, and support services to Filipinos living with HIV;
(2) adopt a multi-sectoral approach to respond to the HIV and AIDS situation in the Philippines through the utilization of a whole government approach, the local communities, as well as civil society organizations;
(3) ensure access to HIV- and AIDS-related services through the elimination of stigma and discrimination towards HIV and AIDS status in the Philippines; and
(4) eradicate and address conditions such as but not limited to poverty, gender inequality, marginalization, and ignorance which escalate the spread of HIV infection.

RA 11166 repeals the previous RA 8504 (Philippine AIDS Prevention and Control Act of 1998), and amends the age of consent as stipulated by RA 8353 (Anti-Rape Law of 1997) and the Revised Penal Code of the Philippines. However, the amendment only covers HIV testing for the “Mature Minor”. RA 11166 also mandates the reconstitution and streamlining of the Philippine National AIDS Council (PNAC), which was established under Section 43 of the RA 8504, to improve the country’s HIV and AIDS response.

Definition of Oral PrEP in the Law

The *Section 3(gg)* of the RA 11166 defines Pre-exposure Prophylaxis (PrEP) as the *"use of prescription drugs as a strategy for the prevention of HIV infection by people who do not have HIV and AIDS."* It is an optional treatment, which may be taken by people who are HIV-negative but who have substantial, higher-than-average risk of contracting an HIV infection.

The Implementing Rules and Regulations (IRR) provides the guidelines, procedures and standards for the implementation of RA 11166 to ensure and facilitate compliance with its provisions. This guideline specifies the role of the National HIV, AIDS and STI Prevention and Control Program (NASPCP), a deciding body under the Disease Control and Prevention Bureau (DPCB) of DOH which is composed of medical experts in the subject of HIV/AIDS and STIs. Together with PNAC, they propose implementation strategies for HIV/AIDS and STI response in order to decrease rates of transmission and social impact. One intervention discussed in the RA 11166 is PrEP, hereby defined as *"the use of prescription drugs to prevent HIV among seronegative, and at substantial risk individuals"*. Both RA 11166 and the IRR have not further discussed the specifics of PrEP implementation and guidelines.

Department Memorandum

General Description of the Policy

In January 2021, the Department of Health released Department Memorandum (DM) No. 2021 0017, also known as the "Interim Guidelines on Pre-Exposure Prophylaxis (PrEP) for the Prevention of HIV Infection in the Philippines". This memorandum aims to enhance service delivery of PrEP for people at substantial risk of HIV infection. The proposed guidelines are addressed towards STI and HIV service providers of facilities offering PrEP services from public and private sectors. Specific guidelines are categorized into a six-point approach which includes the following: (1) Programmatic requirements for PrEP service provision; (2) Screening for substantial risk of HIV infection; (3) Initiation of PrEP; (4) Stopping PrEP; (5) Clinical follow-up and monitoring; and (6) Monitoring and evaluation.

Persons at substantial risk of getting HIV

The DOH memorandum lists specific guidelines for the eligibility criteria of HIV screening services for individuals at substantial risk for HIV:

a. Those who engage in sex with a PLHIV who is not virally suppressed or whose results of viral load testing are unknown (e.g., HIV serodiscordant couples);
b. Those having condomless or unprotected anal/vaginal/ or neovaginal sex in the past 6 months with more than one partner;
c. Those with history of STI in the past 6 months (diagnosed, symptoms, or self-report;
d. Those using sex-enhancing drugs or non-sterile injecting equipment in the past 6 months;
e. Those who have used HIV PEP for sexual exposure in the past six months;
f. Those who have a sexual partner with one or more HIV risk factors in the past 6 months; and
g. Those who requested PrEP

Oral PrEP Regimens

The following clinical indications must be considered before an individual becomes eligible for PrEP:

a. Must be HIV negative;
b. Must be free of signs/symptoms of an acute retroviral syndrome (ARS) with no probable recent exposure to HIV;
c. Must have a good renal function, if known (creatinine clearance > 60 mL/min);
d. Must be free of any allergy or contraindications to PrEP medicines (TDF or FTC)
e. Must weigh at least 35 kg.
f. PrEP has no or minimal drug interactions with commonly prescribed medicines nor significant side-effects. PrEP can be used safely by most people, including pregnant or breastfeeding women, women using hormonal drugs for contraception, or transgender persons on gender-affirmative hormone therapy

Dosing regimen

On the same day clients are confirmed negative for HIV screening, an initial supply of oral PrEP shall be provided. A one-month supply shall be provided at first visit, followed by a 2-month supply at second visit, then a 3-month supply for every succeeding visit. The memorandum further notes that under special circumstances, such as acknowledgment of compliance, more than a 3-month supply may be given.

Oral PrEP shall be taken once to a maximum of twice daily. Use of oral PrEP is especially recommended for periods of frequent or unpredictable sex. Event-Driven PrEP can be considered for infrequent, anticipated, or planned sex.

A single PrEP pill may be continued daily for continuous sex, with a single pill taken 2 days after the last sex act.

The guideline further specifies dosing regimens for starting/restarting oral PrEP. There are also significant differences in dosing strategies for MSMs.

Counselling for oral PrEP

Pre-initiation counselling

Pre-initiation counseling on PrEP is first done to ensure that clients understand how PrEP works, providing the clients adequate knowledge to decide if PrEP is indeed a suitable preventive tool for them.

Follow-up and monitoring

Follow-up HIV screening to monitor status shall be scheduled after 1 month of PrEP intake and at least 3 months thereafter. Individuals with HIV-inconclusive status must discontinue oral PrEP then be retested after 14 days. The client may resume PrEP if a repeat HIV test presents negative. During this period, pertinent lab tests (i.e., serum creatinine test, STI screening, hepatitis C antibody screening) must be done.

As specified by the guideline, counselling must include health promotion on sexual health and the proper use of oral PrEP. Counseling must also include the provision of condoms and lubricant. The clients must always be reminded to consult the clinician if they decide to halt oral PrEP.

Programmatic Considerations for Oral PrEP implementation

Programmatic requirements for PrEP service provision which were listed in the memorandum include the following: (1) human resource to provide counseling, screening, and follow-up monitoring; (2) access to clinicians for scripting and initiation; (3) access to laboratory services for baseline testing and monitoring; (4) commodity management procedures to order, handling and requesting; and (5) monitoring and evaluation systems including documentation, quality assurance, and improvement, and reporting.

The agencies that are responsible for the oral PrEP implementation program are the Disease Prevention and Control Bureau (DPCB), Epidemiology Bureau (EB) and

Centers for Health Development (CHDs). Meanwhile, the local government unit and the public and private sector health facilities and community-based organizations shall ensure the provision of oral PrEP services at their level. Funds will be coming from the National HIV, AIDS, and STI Prevention and Control Program ofthe DPCB and CHDs to ensure that in 2021 and 2022, oral PrEP will be sourced out from HIV projects and grants.

The roll-out of PrEP should also follow a three-year phase approach summarized in Table 10 below.

Table 10. ***Phased Approach on oral PrEP Roll Out*** *(Adapted from DM 2021-0017)*

	Year 1	Year 2	Year 3
Geographic Areas	NCR, Central Visayas, Central Luzon, and select Global Fund and PEPFAR Category A sites. Facilities in other regions which have the capacity and interest to deliver PrEP services.	All other HIV category A cities	Nationwide

Legal Protection of Individuals against Discrimination

Another issue is the legal protection against discrimination on the basis of sexual orientation, gender identity, gender expression, or HIV status, which can affect access to oral PrEP and adjunct services. There are existing nondiscrimination provisions embedded in the Philippines in RA 11166. Section 50 of RA 11166 lists the corresponding penalties that will be incurred by healthcare workers, employers, businesses, and any persons who engage in discriminatory acts. RA 11166 defines discrimination as

> *"unfair or unjust treatment that distinguishes, excludes, restricts, or shows preferences based on any ground such as sex gender, age, sexual orientation, gender identity and expression, economic status, disability, ethnicity, and HIV status, whether actual or perceived, and which has the purpose or effect of nullifying or impairing the recognition, enjoyment or exercise by all persons similarly situated, of all their rights and freedoms"*

In addition, localities enforced ordinances prohibiting discrimination. However, information dissemination about HIV-specific legal protections in the law is still

lacking and key populations are often unaware of their protections against discrimination. There were also accounts of workplace discrimination related to sexual orientation and HIV serostatus. Therefore, strengthening the implementation of legal protection against discrimination can improve health seeking behaviors of key populations who are at high risk of HIV (Adia et al, 2021).

Policy Barriers for Oral PrEP

Obtaining Child Assent and Parental Consent to Access Oral PrEP

A possible policy barrier related to oral PrEP includes the age restrictions to accessing the drug. While RA 11166 amended the age of consent provided by the Anti-Rape Law of 1997 and the Revised Penal Code, it is noted that the promulgations of RA 11166 only cover HIV testing among adolescents aged 12 years to less than 18 years old. No specific stipulations were identified regarding the role of the Mature Minor Doctrine (*see details in the section of "Other Laws with Indirect Impact to Oral PrEP")* for accessing oral PrEP.

Barriers to Accessing Oral PrEP among Key Populations

One potential issue when it comes to accessing oral PrEP is the legal approach and attitudes towards individuals who exchange sex for money and persons who use drugs (PWUDs) as user of this regimen. They are often marginalized and overlooked when it comes to HIV services (Shea et al., 2019; United Nations, 2018; UNAIDS, 2021; Platt et al., 2018; cited in UNAIDS, 2021; Healey, 2018; cited in UNAIDS, 2021). Human rights violations against sex workers are more prevalent in countries criminalizing sex work such as the Philippines. Moreover, the criminalization of drug use creates a barrier for these populations who need to access PrEP and other HIV services. Because of these, individuals who exchange sex for money and PWUDs become hesitant to access healthcare in fear or being arrested or reported resulting from the strict enforcement of a criminal approach to drugs.

Per the Dangerous Drugs Act of 2002 (RA 9165), law enforcers are mandated to arrest suspected individuals because being involved in the drug trade and using illegal substances are considered as crimes against the state. The Revised Penal Code, on the other hand, identifies "prostitutes" as criminals, in which it further elaborated that "for the purposes of this article, women who, for money or profit,

habitually indulge in sexual intercourse or lascivious conduct, are deemed to be prostitutes (Chapter 2, Article 202)".

So, if an individual's risk for getting HIV is because they are involved with the use of illegal substances or exchange of sex for money, this individual will be less likely to access oral PrEP and other adjunct services. Individuals from these two populations are likely to hide, even from health facilities, because of the fear of being arrested (Commision on Human RIghts - Philippines; cited in United Nations, 2018).The lack of legal protection for these marginalized subpopulations discourages them from accessing services such as oral PrEP (Decker et al, 2015; cited in UNAIDS, 2021).

Other Laws with Indirect Impact to Oral PrEP

Use of HIV Prophylaxis during Sexual and Reproductive Health Emergencies and Disasters

AO 2016-0005 is a health policy concerning the provision of a service package for sexual and reproductive health during health emergencies and disasters. It recognizes that the need for sexual and reproductive health services do not stop, even when health emergencies happen. The objectives of the law are as follows:

(A) To provide guidelines to all concerned agencies and stakeholders on the implementation of the Minimum Initial Service Package (MISP) for Sexual and Reproductive Health (SRH) during emergencies and disasters.
(B) To define the core package that will constitute the MISP for SRH during emergencies to be integrated in the DOH essential service package for emergencies.
(C) *To create the national Reproductive Health Coordinating Team (RHCT) that will coordinate the implementation of the MISP for SRH during emergencies.*

This policy recognizes that a set of priorities related to sexual and reproductive health must be identified and that key interventions are based upon the recommendations of Project SPHERE. In one of its specific guidelines, STIs, HIV and AIDS are highlighted as an areas with the following stipulations: (1) Provide access to free condoms; (2) Strictly adhere to universal precautions, e.g. rational and safe blood transfusion. (3) Provide anti-retrovirals (ARVs) for those undergoing treatment (4) Provide syndromic treatment of STIs. This AO highlights the need for HIV prevention during disasters. While the policy does not specifically mention the use of oral PrEP in its guidelines, it delineates the need for HIV prophylaxis when a potential exposure happens within the last 72 hours.

The Mature Minor Doctrine and Consent for HIV Testing

Section 3(bb) of the RA 11666 defined the Mature Minor Doctrine as the legal principle which states that minors can independently decide for themselves to receive any medical procedures given that they have been assessed and informed by the healthcare professional on the nature of the medical procedure.

Further, in keeping the principle of the Mature Minor Doctrine, Section 29 (HIV Testing) of the RA 11166 stipulated the following circumstances when HIV testing will be acceptable for minors to decide:

a. If the person is 15 to 18 years of age, consent to voluntary HIV testing shall be obtained from the child without the need of consent from a parent or guardian;
b. If a child is below age 15 who is pregnant or engaged in high-risk behavior, he or she shall be eligible for HIV testing and counseling, with the assistance of a licensed social worker or health worker. Consent to voluntary HIV testing can be obtained from the child without the need of consent from a parent or guardian; and
c. If a child is below 15 or is mentally incapacitated, consent to voluntary HIV testing shall be obtained from the child's parent or legal guardian.

While the law is clear about how a mature minor can access HIV testing with the assent of a social worker or a health worker, the law was not able to clarify if the mature minor can also access oral PrEP even without the consent of their guardian or parent.

EVIDENCE FROM FOCUS GROUP DISCUSSIONS

Focus group discussions (FGD) among (1) the potential users and (2) HIV program implementers and health system experts were conducted by the HTAC and HTAU in 26 October 2021 and 27 October 2021, for their perspectives on the use of PrEP and how it is expected to affect the implementation of oral PrEP and HIV strategies in the Philippines.

Objectives and participants of the FGDs:

FGD1 : Potential Users

Objectives:

- To identify potential users' perceived barriers and benefits in the use of oral PrEP
- To identify potential users' perceived barriers and benefits in the implementation program of oral PrEP
- To identify the other issues about oral PrEP

*Inclusion criteri*a (derived from DM 2021-0017):

- Persons who have used or are currently using oral PrEP
- Persons who have not used oral PrEP, but are willing to explore the use of oral PrEP
- Persons who have exchanged sex for money and/or incentives
- Men having sex with other men
- Persons who are sexually active
- Persons who have multiple sexual partners

DOH Department Memorandum 2021-0017 section on screening for people at substantial risk for HIV infection became the basis for the inclusion criteria for FGD 1. People with at least one of these criteria were considered at high risk of getting infected by HIV. Moreover, since oral PrEP is targeted towards HIV seronegative populations, the sole criterion for exclusion was if a potential participant is a person living with HIV (PLHIV).

FGD2 : HIV Program Implementers

Objectives:

- To identify the perceived factors that could facilitate the implementation of oral PrEP.
- To identify the perceived implementation barriers in the administration of oral PrEP.

- To identify the perspectives of program implementers on the possible ethical, social, and legal issues that could arise when oral PrEP is made available to intended patients.

Inclusion criteria: organizations were recruited based on their HIV or gender advocacy. Accredited professional organizations and other non-government organizations were invited for their perspectives on HIV program implementation in the Philippines.

For more details on the FGDs conducted, please refer to the full report entitled *Oral PrEP ELSHI report* in Appendix 2.

Key findings from the FGDs

THE NEED FOR ORAL PREP

It is evident from both FGDs that oral PrEP is needed as part of the HIV preventive strategies being implemented and provided in the Philippines. Non-inclusion of oral PrEP for HIV can bind at-risk individuals to the limited number of HIV preventive strategies currently being implemented in the Philippines. Since there are individuals who opt not to use condoms or other existing preventive strategies, the non-inclusion of PrEP can restrict both the general and at-risk individuals from achieving better health outcomes. The following themes discuss issues stemming from this need.

OUTCOME 1: Ethical and Social Impact

There is a clearly identified need for oral PrEP, according to the participants from both groups. Both potential users and implementers agreed that, upon inclusion of oral PrEP to the PNF, social stigma on oral PrEP use (e.g., censoring of terms related to HIV; perceiving that the use of oral PrEP would supposedly lead to promiscuity; HIV services-related discrimination; poor health-seeking behavior) may still ensue. Health system and program implementation changes for oral PrEP must be streamlined or scaled up so these societal implications can be addressed. These changes included community mobilization activities (*e.g., participation of members of the community in policy-making and the program cycle for oral PrEP*), multi-population level capacity building for oral PrEP, and oral PrEP streamlining / institutional scaling up, among others.

In addition to that, what hinders social support and perpetuates stigma is the lack of participation in oral PrEP initiatives, and lack of awareness of HCWs and peers

of oral PrEP recipients. While the community mobilization was highlighted for both FGD groups, the framing of purpose between potential users and the implementers differ. Potential users frame their purpose as a way to increase social support, while implementers focus on mobilizing people at the level of the community and improving knowledge, skills, and attitudes to address the population-level risks (e.g., increased incidence of other STIs) associated with oral PrEP use. Community mobilization activities which were identified in both FGDs included community discussions on what should be the provisions to be included in oral PrEP policies / guidelines, and delegation of key actions on oral PrEP program planning, implementation, monitoring, and evaluation.

Themes specifically emerging from the potential users stem from the socio-cultural determinants of health and how personal experiences can affect oral PrEP use. Personal experiences from the potential users emphasized the overarching role of their social and cultural context to their experience of HIV services in the Philippines. Spillovers of gender-related issues and neoliberalism, intertwining with existing conservative societal perceptions on HIV, establish barriers to accessing oral PrEP.

On the other hand, themes observed from implementers are directed towards the risk mitigation for oral PrEP. As implementers, they were mostly concerned on how oral PrEP can mitigate risks of HIV in groups of individuals, whilst addressing other emerging risks that may happen upon integration of oral PrEP into communities.

OUTCOME 2: Legal Impact

No themes related to legal implications were generated from the potential users. In the case of program implementers, overall, they agree that there is a pressing need to provide oral PrEP to minors. This is especially true for minors who are at high risk of getting HIV. Eligibility of minors to procure oral PrEP is a legal issue that implementers raised as needing urgent resolution.

OUTCOME 3: Health Systems Impact

Both groups touched on health education for oral PrEP. However, for users, the focus is on using various forms of health education and capacity-building to align maladaptive societal beliefs on HIV and oral PrEP. Implementers sought to

capacitate as many different sectors of the population as possible. They argued that when representatives of various sectors are capacitated, these representatives could echo the appropriate knowledge, skills, and attitudes on HIV and oral PrEP.

Potential users identified financial-related factors why they would not get oral PrEP, but implementers were concerned more for the costs of direct non-medical and indirect costs for oral PrEP. The potential users pointed out that poor health-seeking behaviors are a result of personal financial priorities. On the other hand, coverage for other costs related to using oral PrEP were more crucial for the implementers—these costs included the diagnostics and therapies. Implementers were keen on protecting individuals from financial risk by expanding the healthcare coverage of potential users to include oral PrEP and other HIV preventive strategies.

To ensure that oral PrEP will be implemented successfully, changes in the health system processes must be done, as highlighted by both potential users and implementers. The actual processes that need to be changed, however, differed among the two groups. Potential users wanted oral PrEP to reach communities more efficiently by integrating oral PrEP initiatives as a part of existing health system processes. On the other hand, implementers agree that strengthening components of the Philippine health system (e.g. service delivery, interprofessional collaboration, increasing rural/GIDA access to oral PrEP, etc.) will make it easier to include recommendations for the use of oral PrEP in the service delivery.

The target individuals of oral PrEP differed between the two groups. While potential users wanted oral PrEP to be accessible outside of the usual key affected populations (e.g., MSMs, LGBTQIA+), implementers wanted to do away with identifying populations and recommended establishing a system of providing oral PrEP based on the actual risks unique to each individual.

Cost-effectiveness

According to the *Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring: Recommendations for a Public Health Approach* (WHO, 2021), the HIV incidence threshold for cost-saving implementation of oral PrEP will vary depending on the *(1) relative costs of oral PrEP (TDF-based regimens) versus the treatment for HIV infection;* and, *(2) the anticipated effectiveness of oral PrEP*. Depending on the situation (e.g., areas with good implementation strategies), oral PrEP may or may not be more cost saving than other interventions, but the value of being HIV-free is intangible and cannot be measured by monetary value, regardless of HIV incidence in the community. From the 2016 guidelines to the 2021 guidelines, the WHO retained its position on the cost-effectiveness of oral PrEP —in places where the incidence of HIV is greater than 3 per 100 person-years, offering oral PrEP is generally expected to be cost-saving in many situations. The cost–effectiveness of oral PrEP may decrease with declining HIV incidence in the context of universal treatment for HIV; but primary prevention, including oral PrEP, is essential to eradicate HIV, regardless of cost–effectiveness. In the Philippines, the current incidence per 1000 population across all ages is 0.15 [0.14-0.17] (UNAIDS, 2021). Philippine HIV incidence rate data per 100 person-years is currently not available in the modelling tool containing the data on prevalence and incidence for PLHIV (i.e., HIV AEM - Spectrum Estimates).

Additionally, a systematic review of cost-effectiveness modelling studies by Gomez et al. (2013) found that, in generalized epidemics, giving priority for oral PrEP use (regardless if TLD-based or not) to people at substantial risk of acquiring HIV infection increases impact on cost-effectiveness in terms of prioritization (i.e., by age group or by risk factors), adherence, behavior change, toxicity, and resistance. Of the 13 economic evaluation studies included, two (2) [Gomez et al, 2012; & Alistar et al, 2014] were on LMICs.

- **Gomez et al. (2012)**

  Study Description

  This is a mathematical modelling study with a health provider perspective based on the US Center for Disease Control and Prevention interim guidelines for PrEP, following a 10-year time horizon using a deterministic, compartmental model to represent the sexual transmission of HIV amongst MSM and transwomen in Lima, Peru (as a test case). The study aims to provide information on the impact of a feasible intervention and to determine the most efficient strategies (i.e., oral PrEP

conditional efficacy [reduction in susceptibility to HIV infection during a PrEP-protected sex act], coverage, prioritisation strategy, and time to scale up—and risk compensation behaviour) for its roll out in this population to assist the process of translating recent trial results into cost-effectiveness programs. The intervention scenarios being compared in this study are shown in Table 12.

Table 12. *Summary of intervention scenarios (Gomez et al, 2012).*

<table>
<tr><th>Scenario</th><th>Intervention</th></tr>
<tr><td>1</td><td>Oral PrEP
<table>
<tr><th></th><th>Coverage</th><th>Distribution Type</th></tr>
<tr><td>1a</td><td rowspan="3">Low (5%)</td><td>Uniform</td></tr>
<tr><td>1b</td><td>Some prioritization</td></tr>
<tr><td>1c</td><td>High prioritization</td></tr>
<tr><td>1d</td><td rowspan="3">High (20%)</td><td>Uniform</td></tr>
<tr><td>1e</td><td>Some prioritization</td></tr>
<tr><td>1f</td><td>High prioritization</td></tr>
</table>
<u>Notes:</u>
Low coverage: 5% of uninfected individuals use PrEP
High coverage: 20% of uninfected individuals use PrEP
Uniform prioritization: PrEP distributed evenly to all MSM and transwomen
Some prioritization: Higher coverage is achieved in key populations such as the transwomen at higher risk and sex worker groups (but no more than 50% coverage) than in MMSW and MMSM
High prioritization: Once 90% of the transwomen at higher risk group receives PrEP, the residual amount (to achieve 5% or 20% overall coverage) is divided among the three other populations, prioritising sex workers over MMSW and MMSM</td></tr>
<tr><td>2</td><td>Female sex worker outreach</td></tr>
<tr><td>3</td><td>Voluntary counselling and testing</td></tr>
<tr><td>4</td><td>Condom use</td></tr>
<tr><td>5</td><td>STI treatment</td></tr>
<tr><td>6</td><td>Men having sex with men outreach</td></tr>
<tr><td>7</td><td>HAART</td></tr>
</table>

Particularly, the study looked into the impact of coverage (i.e., low vs. high), adherence to oral PrEP, and prioritization of key groups (i.e., sex workers, transwomen) on both health benefits (measured as DALYs averted) and costs to the health system. The discounting rate for future costs, savings, and health gains is 3%.

For the input data on costs, the following costs were included: *(1) HIV testing before starting oral PrEP; (2) HIV testing every 3 months during use of oral PrEP; (3) HIV confirmatory testing for positive cases; (4) one creatinine/blood urea nitrogen test per year during oral PrEP use; (5) outreach and counselling services; and (6) condom and lubricant promotion and provision.* The unit cost of oral PrEP intervention was based on the cost data provided by Gilead (2012) for 1 month supply (1 bottle), and was estimated to be between 525 USD and 830 USD (over two-thirds of the cost estimate was from the cost of oral PrEP drugs). These costs were measured in the year 2012.

For the input data on the efficacy of oral PrEP, this study assumed an efficacy of 92% (95% CI 40-99%), which was based on iPrEx. We note that the efficacy used in the study is much higher than the computed efficacy (i.e. 56%; 95% CI: 28-73%) from the relative risk found in the systematic review of Chou et al (2019) as reported in *Section C2: Clinical Effectiveness and Safety* of this evidence summary.

For the incidence data used in the modelling study, they assumed an incidence of 3.5 infections per 100 person years for all high risk MSM, and 2.2 infections per 100 person years for all MSM.

The principal epidemiologic outcome in the analysis was the cost per disability-adjusted life year (DALY). The estimated number of DALYs associated with one HIV infection averted was calculated as the sum of the number of years of life lost and the number of years lost due to disability using published methods. For the first threshold, they referred to the WHO Choosing Interventions That Are Cost-Effective (WHO-CHOICE) initiative which considers an intervention to be *(1) very cost-effective, if its cost is less than the gross domestic product (GDP) per capita (<5,401 USD) per DALY averted*; *(2) cost-effective, if it costs between one and three times the GDP per capita (5,401 USD to 16,203 USD) per DALY averted; or (3) not cost-effective, if it costs more than three times the GDP per capita (>16,203 USD) per DALY averted*. The 2020 GDP per capita in the Philippines was at 3,298.8 USD (The World Bank, 2021). Meanwhile, the GDP per capita in the Philippines is expected to reach 3,160.00 USD by the end of 2021 (Trading Economics, 2021). The second threshold system used a more conservative cutoff point suggested by the World Bank in 1993 for middle-income countries: *(1) 100 USD per DALY averted to reflect a highly cost-effective intervention, (2) between 100 USD to 500 USD for a cost-effective intervention, and (3) 500 USD for an intervention to be considered not cost-effective*. Currently, there are no updated cost-effectiveness thresholds from the World Bank.

However, according to Woods, et al (2016), initial estimates for purchasing power parity-adjusted cost-effectiveness thresholds include USD 606 - 3,358 for the Philippines and USD 1,969 - 7,747 for Peru. The cost per DALY averted was quantified for PrEP interventions assuming three levels of adherence rate based on the iPrEx open-label trial (ie., good, average, poor).

Key Findings

Across all scenarios, the highest estimated cost per DALY averted is below the WHO-CHOICE threshold for a cost-effective intervention for Peru (<5,401 USD/DALY averted). Meanwhile, only the prioritization scenarios *(some prioritization and high prioritization)* at low coverage, and the low bound of a high prioritization scenario at high coverage, are likely to be cost-effective using the more conservative threshold suggested by the World Bank (<745 USD/DALY averted).

Table 13. Summary of highest estimated cost per DALY across scenarios.

Scenarios		Cost per DALY averted (USD)	Cost effective based on **WHO threshold** (< 5,401 USD/DALY averted)?	Cost effective based on **WB threshold** (<745 USD/DALY averted)?
Coverage	Prioritization			
Low (5%)	Uniform	1,702	Cost-effective	Not cost-effective
	Some	707	Cost-effective	Cost-effective
	High	637	Cost-effective	Cost-effective
High (20%)	Uniform	1,779	Cost-effective	Not cost-effective
	Some	1,400	Cost-effective	Not cost-effective
	High	1,052	Cost-effective	Not cost-effective

- None of the scenarios appear to be cost-effective when the lower bound of PrEP conditional effectiveness (i.e., 40%) is included in the analysis, nor are the scenarios considered very cost-effective using the World Bank threshold. However, the cost per DALY averted is substantially reduced with a high degree of prioritization. Moreover, the study found out that, depending on the

implementation strategy, PrEP could be as cost-effective as treatment for sexually transmitted infections, MSM outreach, or highly active ART.

- Overall, they concluded that a strategic PrEP intervention could be a cost-effective addition to existing HIV prevention strategies for MSM populations. However, despite being cost-effective, considerable expenditures and human resources will still be required to generate a significant reduction in incidence. These expenditures should not be considered unless well-performing ART services are already in place.

- **Alistar, Owens, & Brandeau (2014)**

  Study Description

  This is a cost-effectiveness study with a 20-year time horizon using a dynamic compartmental model of the HIV epidemic in a population of non-injection drug users (non-IDU), IDUs who inject opiates, and IDUs in methadone maintenance treatment (MMT), adding an oral PrEP program (i.e., TLD + 3TC) for uninfected IDUs in Ukraine. The interventions compared in the cost-effectiveness study are: the use of oral PrEP along with the status quo (i.e., PrEP + ART) versus the status quo. Under the status quo, approximately 22% of eligible HIV-infected individuals receive ART, virtually no IDUs receive MMT, and no IDUs receive PrEP.

  For the input data on efficacy, this study assumed an efficacy of 10-72% for PrEP, 10-90% for ART, and 60-99% for MMT. Other parameters were also considered in the model: HIV prevalence, injection behavior, sexual behavior (i.e., number of partners, condom usage rate), and access to antiretroviral therapy. HIV Prevalence among those aged 15-49 years is 0.99% [0.73%–1.16%] for non-IDUs and 41.2% [17.3%–70.0%] for IDUs.

  For the input data on the costs, they considered non-HIV medical care, HIV care, ART (including IDU services), MMT and PrEP (including counselling services). The year the cost values were measured was not stated. The cost values were measured in the year 2013.

  The study measured health care costs, quality-adjusted life years (QALYs), HIV prevalence, HIV infections averted, and incremental cost effectiveness using a societal perspective which considered all health care costs and savings, regardless

of the source or beneficiary. Additional costs include an annual health care cost of 311 USD for all individuals and annual HIV care costs of 1,200 USD for all HIV-infected individuals (UNAIDS, 2008). Furthermore, the study discounted costs and QALYs to the present at 3%. The cost-effectiveness threshold applied in the study is approximately 7,400 USD, which was based on the GDP per capita of Ukraine as per WHO criteria.

Key Findings

Based on the results, strategies of oral PrEP alone, oral PrEP combined with MMT alone, or oral PrEP combined with ART are **inferior** to strategies of MMT alone or MMT combined with ART. The most cost-effective strategy is MMT alone, with an incremental cost-effectiveness ratio (ICER) of approximately 520 USD/QALY gained compared to the status quo, as shown in Table 14.

Table 14. ***Summary of ICER values across different interventions.***

Intervention		ICER (USD/QALY gained)	Cost-effective based on the CE threshold (7,400 USD)?
Single Interventions	25% PrEP	1,379	Cost-effective
	50% PrEP	1,411	Cost-effective
	ART	985	Cost-effective
	MMT	517	Cost-effective
Dual Interventions	MMT, 25% PrEP	963	Cost-effective
	MMT, 50% PrEP	1,094	Cost-effective
	MMT, ART	780	Cost-effective
	ART, 25% PrEP	1,102	Cost-effective
	ART, 50% PrEP	1,156	Cost-effective
All Interventions	MMT, ART, 25% PrEP	1,000	Cost-effective
	MMT, ART, 50% PrEP	1,084	Cost-effective

Comparator: status quo (*i.e., no scale up of ART and MMT)*

Adding oral PrEP to a portfolio that includes MMT (at 25% coverage) and ART (at 80% coverage) costs approximately $1,700/QALY gained for 25% oral PrEP coverage and $2,300/QALY gained for an additional 25% oral PrEP coverage (thus 50% total coverage) – amounts that would be highly cost effective in this setting.

Sensitivity analysis found that a combination of oral PrEP for 50% of IDUs and MMT lowered HIV prevalence the most in both IDUs and the general population. ART combined with MMT and oral PrEP (50% access) averted the most infections (14,267). For an oral PrEP cost of 950 USD, the most cost-effective strategy was MMT, at 520 USD/QALY gained versus no intervention. The next most cost-effective strategy consisted of MMT and ART, costing 1,000 USD/QALY gained compared to MMT alone. Further, adding oral PrEP (25% access) was also cost effective by World Health Organization standards, at 1,700 USD/QALY gained. Oral PrEP alone became as cost-effective as MMT at a cost of 650 USD, and cost saving at 370 USD or less.

In summary, the authors concluded that oral PrEP for IDUs can be part of an effective and cost-effective strategy to control HIV in regions where injection drug use is a significant driver of the epidemic. Where budgets are limited, focusing on MMT and ART access should be the priority, unless oral PrEP has low cost. Note that in this study, the estimated cost of oral PrEP is at 950 USD per year, ranging from 100 USD to 1,500 USD.

Overall, the cited economic evaluation in a low-middle income setting has concluded that oral PrEP can be cost-effective, areas where injection drug use is a significant driver of the epidemic (Alistar, Owens, & Brandeau, 2014). Alistar et al. (2014)'s analysis demonstrated that oral PrEP alone is inferior to strategies of MMT and ART alone but is still cost-effective according to WHO.

While these studies show potential value for money of implementing oral PrEP, results cannot be directly adopted and be inferred for the Philippine context because of the differences in the assumed efficacy, the cost of oral PrEP, and HIV incidence applied in these model settings.

Affordability & Viability

This section presents the 1-year comparative costing and 5-year budget impact of using oral PrEP for individuals at substantial risk of acquiring HIV.

Inputs to the costing analysis

Cost items

The intervention in our costing analysis consists of the cost of the drug regimen on oral PrEP, the cost of monitoring adverse drug reactions (ADRs), and the cost of other HIV preventive strategies to which oral PrEP shall be delivered with.

The cost of monitoring of ADRs included the creatinine test as studies have shown that oral PrEP is associated with an increased risk of renal injury (Yacoub et al, 2016; Ascher et al, 2020).

Lastly, the other HIV preventive strategies to which oral PrEP shall be delivered alongside with are non-pharmacologic interventions (NPIs), which consisted of the following strategies: (1) advocacy of undetectable = untransmittable (U=U) messaging; (2) promotion and provision of condoms and lubricants; and (3) community and online outreach.

The comparator in our costing analysis consists of the NPIs currently being implemented by the HIV program for their preventive strategies.

For the five-year costing analysis which involved all the target users for five years, we also considered the cost of HIV treatment for those who will proceed to HIV positive state. This cost included the cost of first-line HIV treatment (ART) [i.e., cost of Tenofovir/Lamivudine/Dolutegravir (TLD)]; and, the cost of *Outpatient HIV/AIDS Treatment (OHAT)* package by PhilHealth, which covers the following services according to the PhilHealth Circular No. 011-2015: medicines, laboratory examinations, monitoring for ARV toxicity, and professional fees.

Resource utilization

The current treatment regimen for PrEP is daily oral PrEP, and it may be given to any individual considered to be at substantial risk of acquiring HIV. For MSM, it can be provided as a (1) daily oral PrEP during periods of frequent sex or; via (2) event-driven

PrEP (ED-PrEP) for infrequent, anticipated or planned sex. ED-PrEP is given using two pills as a loading dose between two and 24 hours before sex, then a third pill taken 24 hours after the first two pills, and a fourth pill 48 hours after the first two pills. MSM can switch between daily and ED-PrEP based on changes in their sexual practices (DM 2021-0017). Since ED-PrEP data are limited in other populations, this dosing is currently not recommended in other groups (WHO, 2019). Individuals can consider stopping oral PrEP if they are no longer at a substantial risk of acquiring HIV infection. In this costing analysis, we calculated based on a daily oral PrEP regimen and assumed that the duration of drug utilization lasts for 6 months which is based on the duration of oral PrEP use where adherence remains to be high (80%), as reported by *Love Yourself, Inc*. in their consultation report. We note that this duration of use is relatively higher compared to the worldwide benchmark on oral PrEP use which is 3 months, according to the same consultation report by *Love Yourself, Inc*.

Meanwhile, a scenario wherein MSM will use ED-PrEP was not calculated in this costing analysis since while there is available data on the estimated number of users following this regimen, there is no data on their average regimen/ usage that we can assume for the ED-PrEP costing scenarios.

For the frequency of use of the creatinine test to monitor for possible ADRs, the program mentioned that it shall be done every 6 months or as indicated for all PrEP users, especially for those with a history of conditions affecting the kidney, such as hypertension and diabetes. For the costing analysis, we assumed a frequency of once every 6 months for all oral PrEP users.

Meanwhile, each NPI strategy shall be implemented for the whole year based on the *2015 Size Estimation of Key Populations in the Philippines* by DOH EB.

The resource utilization for TLD therapy is based on the standard treatment regimen based on the current HIV treatment guidelines (i.e., one tablet daily) . As for the OHAT package, the claims can be availed quarterly according to the PhilHealth Circular 011-2015.

Cost value

A single bottle of oral PrEP is priced at PhP 1,500, which contains 30 tablets and is good for a month, following a once-daily dosing regimen. Hence, each user will need 6 bottles in 6 months amounting to a total of PhP 9,000 or USD 178.63 (based on

BSP [2021] conversion rate of PhP 50.405 per USD 1). The unit cost of one bottle of oral PrEP was based on the *Global Fund PR Supply Chain Manager*.

Meanwhile, the cost of monitoring of ADR per user is PhP 187.50 (USD 3.72), which was based on the average price of creatinine test from selected DOH hospitals (i.e., Southern Philippines Medical Center, Cebu South Medical Center), as indicated by the NASPCP in their costing inputs submission.

Overall, the annual total cost of the non-pharmacologic HIV preventive interventions to which oral PrEP shall be delivered with is PhP 70.66 M. Advocacy of undetectable = untransmittable (U=U) messaging costs PhP 1.55M while promotion and provision of condoms and lubricants is worth PhP 68.44M. Lastly, community and online outreach is PhP 0.67 M. The costs of the strategies were based on actual program implementation costs, indicated in the *Philippine Health Sector HIV Strategic Plan Costing Worksheet* and *2019 and 2022 Project Procurement Management Plan (PPMP)*.

The cost value of TLD is based on the Procurement Plan of the program, which costs PhP 6,588.00 yearly. Meanwhile, the PhilHealth Outpatient HIV/AIDS Treatment (OHAT) package costs PhP 30,000.00 yearly or PhP7,500.00 quarterly.

Additional costing details are reflected in Table 16.

Number of Target Population

Two sets of target population were used in the costing analysis based on two sources: (1) the total target number of users set by the program, and (2) the total number of seronegative individuals at substantial risk, which is defined as target recipients of oral PrEP per DOH DM 2020-0017.

Scenario 1: Target number of users set by the Program based on enrollment rate

According to the program, the target number of individuals for oral PrEP was 10,000 which is 1.73% of the 578,300 seronegative individuals at substantial risk for HIV. Their target population was set low (i.e, 1%) instead of their ideal target which is 6% of MSM and TW who “ever had anal sex” and never used a condom despite having access and knowledge on its benefits in reducing the risk of HIV as per the Integrated HIV Behavioral and Serologic Surveillance.

The setting of the lower target was based on the rate of enrollment and retention of oral PrEP users in other countries. Table 15 shows the target number of users for the next 5 years which was set by the Program and the other funding agencies providing support on the provision of oral PrEP in the Philippines.

The target number of users to be funded by the program was set to gradually increase as the NASPCP aims to increase its cost sharing with international partners. By 2024, the program aims to subsidize all the total target users (10,000).

Table 15. ***Target number of users by funding source in the next 5 years.***

Year of Implementation	Funding Source	Number of Users
Year 1 (2022)	Government Fund	2,500
	Global Fund	4,500
	PEPFAR Fund	3,500
Year 2 (2023)	Government Fund	4,700
	Global Fund	1,300
	PEPFAR Fund	4,000
Year 3 (2024)	Government Fund	10,000
Year 4 (2025)	Government Fund	10,000
Year 5 (2026)	Government Fund	10,000

Scenario 2: Target number of users based on the number of Seronegative Individuals at Substantial Risk

The assessment team also performed the costing for the number of potential users given the indication of oral PrEP. Based on the projection of DOH-EB, the number of seronegative individuals at substantial risk for the first year is at 578,300.

The projection of the number of seronegative individuals at substantial risk (by the program) for the succeeding years was computed based on the *2015 Key Population Estimates* subtracted by the number of diagnosed MSM 18+

years old and living with HIV, and multiplied by the proportion of MSM eligible for PrEP from the Integrated HIV Behavioral and Serologic Surveillance 2018. The program also mentioned a 9.4% discontinuation rate and no cases of seroconversion. Among the 829 PrEP users with at least one follow up visit, there were 118 who experienced side effects. Among them, 5 out of 118 users discontinued the use of oral PrEP.

Results of the costing analysis

Cost per user for one year

Overall, the total cost of oral PrEP drug regimen and the cost of ADR monitoring, per user per year is **PhP 9,187.50**. Meanwhile, the cost of NPIs alone per individual is estimated at **PhP 77.17.** Hence, the total cost of the intervention per user per year (i.e., sum of pharmacologic and NPIs) is **PhP 9,264.67.**

Clearly, the main driver of cost per user is the cost of oral PrEP.

Table 16. ***Cost per User: Comparative Costing table for oral PrEP + NPI vs NPI alone.***

Parameter	*Intervention* **Oral PrEP w/ ADR monitoring + Non-pharmacological interventions**		*Comparator* **Non-pharmacological interventions only**	
	Inputs	**Reference**	**Inputs**	**Reference**
Part I. Costing of drug regimens (per user)				
Unit cost of oral PrEP: Tenofovir disoproxil phosphate/ Emtricitabine (PhP)	PhP 1,500 per bottle (1 bottle = 30 tabs)	*Initial cost was based on the expert opinion of the Global Fund PR Supply Chain Manager (Estimated based on international price and importation costs)* *Additional local article reference: https://cnnphilippines.com/life/culture/2019/12/1/HIV-PrEP.html*	[redacted]	
Number of dosage units per course of drug regimen	1 tab per day	*DM 2021-0017, pp. 3-4*		
Duration of treatment	6 months	*Project PrEPPY Local Dissemination and Multi-Stakeholders Forum, p. 16*		

		Retention in care outcomes for HIV pre-exposure prophylaxis implementation programmes among MSM in three US cities	
Sub-Total (PhP) for Drug Regimen Cost **[A]**	**PhP 9,000**		
Part II. Other cost items related to monitoring of adverse drug reactions for Oral PrEP (per user)			
Hospitalization cost (PhP)	0.00	N/A	
Monitoring of ADRs (PhP)	187.50 Note: Testing is done once every 6 months for all PrEP users	*Average fee for creatinine test:* *https://tdh.doh.gov.ph/index.php/rates-and-fees* *https://spmc.doh.gov.ph/rates-and-fees/laboratory-rates-and-fees#clinical-chemistry*	
Sub-Total for the cost of ADR monitoring (PhP) **[B]**	**Php 187.50**		
COST OF ORAL PREP THERAPY PER USER (PER YEAR) **[A + B]**	**Php 9,187.50**		
Part III. Costing of non-pharmacologic preventive intervention in the combination strategy (per strategy) *Note: The values are at parity for both Intervention and Comparator. Unit costs correspond to the cost of the strategy in one year, with a target population of 915,700 (DOH EB, 2016).*			
Annual cost of **Strategy 1**: Advocacy of undetectable = untransmittable (U=U) messaging	PhP 1,550,000.00	*Philippine Health Sector HIV Strategic Plan (Costing worksheet)* *2019 and 2022 Project Procurement Management Plan (PPMP)*	*The values are at parity for both Intervention and Comparator.*
Annual cost of **Strategy 2**: Promotion and provision of condoms and lubricants	PhP 68,443,218.00		
Annual cost of **Strategy 3**: Community and online outreach	PhP 70,663,121.00		
Sub-Total (PhP) for all key affected population	**PhP 70,663,121.00**		**PhP 70,663,121.00**
Number of key affected population	**915,700**		**915,700**
Cost of NPI per individual per year	PhP 77.17		PhP 77.17

[C]	*Note: The cost of the non-pharmacologic interventions is the same as its unit cost regardless of the number of users. The value shown here is for illustration purposes only.*	*Note: The cost of the non-pharmacologic interventions is the same as its unit cost regardless of the number of users. The value shown here is for illustration purposes only.*
TOTAL COST PER USER PER YEAR	**PhP 9,264.67** **[COST OF INTERVENTION PER INDIVIDUAL, PER YEAR:** *Cost of Oral PrEP + Cost of ADR monitoring + Cost of NPIs***]**	**PhP 77.17** **[COST OF COMPARATOR PER INDIVIDUAL, PER YEAR:** *Cost of NPIs only***]**

5-year costing analysis: Cost for all target users in 5 years

Scenario 1: *Target users based on the enrollment rate*

In this analysis, apart from the cost of PrEP + NPI in the intervention arm, and cost of NPI in the comparator arm, we also included the cost of HIV treatment for those who will proceed to HIV in the two arms. The baseline transition probability ($TP_{\text{no HIV to HIV in the comparator arm}} = 0.05$) used to calculate the resulting HIV cases in the NPI only arm was derived from Chou et al (2019). The transition probability of the intervention arm ($TP_{\text{HIV to HIV in the intervention arm}} = 0.027$) used to calculate the resulting HIV cases in the PrEP + NPI arm was derived as well from Chou et al (2019). The costs incurred of those who will proceed to HIV includes the cost of TLD and OHAT package which were described in the previous section. It is assumed that users who will not proceed to HIV positive state will continue to use Oral PrEP and NPI in the intervention arm, and NPI only in the comparator arm. For users proceeding to HIV positive state, the cost of treatment (e.g. TLD and OHAT package) was carried over to the succeeding year.

Based on our calculation, from a starting cohort of 2,500 oral PrEP users, 57 HIV cases **worth PhP 2.09 M** can be averted with the use of oral PrEP in the second year. For the succeeding years, 216 to 1167 HIV cases can be averted amounting to cost savings of PhP 7.90 M to PhP 42.70 M

Further, the estimated budget impact to cover the target number of oral PrEP users to be funded by the government is **PhP 23.35 M** in Year 1. The budget difference *(Oral*

PrEP with NPIs VS to NPIs only, including treatment costs) is estimated to be at **PhP 23.16 M** for the entire annual target users for the first year.

For the succeeding four years, a yearly incremental cost of **PhP 63.99 M to PhP 290.64 M** was estimated as presented in **Table 17.**

Note that this calculation only estimates the averted cost of the immediate medical costs incurred for an HIV patient (i.e, TLD treatment and OHAT treatment package). It does not include the succeeding costs related to the probability of the patient proceeding to other HIV sequelae (e.g. opportunistic infections, tuberculosis, among others). As such, it underestimates the cost of illness of HIV, and therefore underestimates the value for money of oral PrEP use as this calculation does not estimate the full cost savings from having HIV. Hence, this simplistic analysis shows a high incremental cost of using oral PrEP in addition to NPIs, compared to NPI alone.

Table 17. *5-year comparative drug costing for target number of users to be funded by the program (*Scenario 1)

Year	Total target users of the program	No. of Averted HIV Cases	Total Treatment Cost of Averted HIV Cases (in PHP)	Calculation without discounting (in PHP)			Calculation with discounting (in PHP)		
				Cost of intervention arm	Cost of comparator arm	Incremental cost	Cost of intervention arm	Cost of comparator arm	Incremental cost
1	2,500	-	-	23,354,596.05	192,921.05	23,161,675.00	-	-	-
2	4,700	57	2,085,516.00	69,141,221.76	5,155,977.39	63,985,244.37	60,390,620.81	4,503,430.34	55,887,190.47
3	10,000	216	7,903,008.00	165,411,938.62	14,315,632.79	151,096,305.83	135,025,414.31	11,685,820.65	123,339,593.65
4	10,000	592	21,660,096.00	271,472,541.78	45,756,415.51	225,716,126.27	207,105,102.33	34,907,350.31	172,197,752.02
5	10,000	1167	42,698,196.00	384,671,639.28	94,028,691.58	290,642,947.69	PP 274,265,562.44	67,041,157.57	207,224,404.87
TOTAL	**37,200**	**2032**	**74,346,816.00**	**914,051,937.49**	**159,449,638.32**	**754,602,299.17**	**676,786,699.89**	**118,137,758.88**	**PhP 558,648,941.01**

Scenario 2: *Target users based on the projected number of seronegative individuals at substantial risk in the Philippines*

In this analysis, the same input parameters used in the previous section were applied, except that that starting cohort is based on the projected number of seronegative individuals at substantial risk in the Philippines.

Based on this calculation, from a starting cohort of 578,300 PrEP users, 13,206 HIV cases worth **PhP 483.18M** can be averted with the use of oral PrEP in the second year. For the succeeding years, 38,761 to 125,166 HIV cases can be averted amounting to cost savings of **PhP 1.42 B to PhP 4.58 B.**

Further, the estimated budget impact to cover the target number of oral PrEP users to be funded by the government is **PhP 5.40 B** in Year 1. The budget difference *(Oral PrEP with NPIs VS to NPIs only*) is estimated to be at **PhP 5.36 B** for the entire annual target users for the first year.

For the succeeding four years, a yearly incremental cost of **PhP 10.16 B to PhP 21.13 B** was estimated as presented in **Table 18.**

As pointed out in the previous section, note that this calculation underestimates the value for money of oral PrEP use as this calculation does not estimate the full cost savings from having HIV. Hence, this simplistic analysis shows a high incremental cost of using oral PrEP in addition to NPIs, compared to NPI alone.

Table 18. 5-year comparative drug costing for projected number of seronegative individuals at substantial risk (Scenario 2)

Year	Total no. of seronegative individuals at substantial risk	No. of averted HIV cases	Total Treatment Cost of Averted Cases (in PHP)	Calculation without discounting (in PHP)			Calculation with discounting (in PHP)		
				Cost of intervention	Cost of comparator	Incremental Cost	Cost of intervention	Cost of comparator	Incremental Cost
1	578,300	-	-	5,402,385,157.53	44,626,496.53	5,357,758,661.00	-	-	-
2	585,700	13,206	483,181,128.00	11,305,887,811.23	1,150,865,315.95	10,155,022,495.29	9,875,000,271.84	1,005,210,337.97	8,869,789,933.87
3	593,000	38,761	1,418,187,468.00	17,123,202,370.78	2,215,730,226.81	14,907,472,143.97	13,977,633,740.84	1,808,695,879.91	12,168,937,860.93
4	600,300	76,222	2,788,810,536.00	23,871,710,788.15	5,327,759,423.94	18,543,951,364.21	18,211,613,863.67	4,064,522,155.47	14,147,091,708.20
5	607,500	125,166	4,579,573,608.00	30,521,601,224.12	9,387,654,269.89	21,133,946,954.22	21,761,479,848.51	6,693,267,752.21	15,068,212,096.30
TOTAL	**2,964,800**	**253355**	**9,269,752,740.00**	**88,224,787,351.82**	**18,126,635,733.12**	**70,098,151,618.69**	**63,825,727,724.86**	**13,571,696,125.55**	**50,254,031,599.30**

Budget Impact to the Program

Scenario 1: Target number of users set by the Program from the enrollment rate

- The 2021 budget of the HIV program is PhP 731,974,590.95. Of this total budget, 7.11% (i.e., PhP 52,500,831.00) is allocated for the existing preventive strategies for HIV.
- The 2022 approved budget of the HIV program is at PhP 773,549,455. Of this amount, 6.30% (i.e., PhP 48,750,000) is allocated for the procurement of oral PrEP. Based on our calculation for the year 2022, the cost of oral PrEP medicines procurement to cover their target users for 2022 (i.e, 2,500 users) will incur PhP 22,968,750.00, denoting that their budget for oral PrEP medicines procurement for 2022 is sufficient for their target users for 2022. For 2023, their projected budget for oral PrEP is PHP 51,187,500, and their target number of users is set at 4,700. Based on our calculations, 4,700 users will incur PhP 43,181,250 cost for oral PrEP medicines, denoting that their budget for oral PrEP medicines procurement for 2023 is still sufficient.
- However, for the years 2024 to 2026, their projected budget for oral PrEP medicines procurement shall not be sufficient to cover their target 10,000 users. Their budget for oral PrEP for 2024 needs to increase by 70.94%; by 62.80 % in 2025; and by 55.05% in 2026, in order to cover the said target number of users for those years. Another option, if the total budget for the HIV program will not increase, is to increase the proportion of oral PrEP medicines procurement budget to the total HIV program budget; however, this will result in disinvestment in some other HIV program interventions or budget items. We note that the total HIV program budget may not necessarily need to increase by the total cost of the oral Prep procurement because of the averted costs of treatment (i.e. TLD drug cost).

  Table 19 shows the projected budget vs the total budget needed to cover their set target of users for scenario 1.

Scenario 2: Target number of users estimated from the total number of seronegative individuals at risk for HIV in the Philippines

- The budget impact of oral PrEP procurement for year 1 is estimated to be PhP 5.38B based on the number of target users

- Budget increase of oral PrEP medicines procurement must be at least 1000% to cover the target number of users from 2022-2026. The increase must be approximately twice the total budget for all HIV preventive strategies to include oral PrEP.

Table 19. ***(Scenario 1) Budget Needed for Oral PrEP for the target number of users VS Projected Budget of the Program for Oral PrEP***

Year	Target number of Oral PrEP users to fund	Total Budget needed to cover the target number of oral PrEP users *(in PHP)*	Projected Budget for oral PrEP *(in PHP)*	Total projected budget of the HIV Program *(in PHP)*	Proportion of oral PrEP budget from the total HIV program budget *(in %)*	INDICATION OF SUFFICIENCY OF BUDGET ALLOCATED FOR ORAL PREP
2022	2,500	22,968,750.00	48,750,000.00	773,549,455.00	6.30	**Sufficient**
2023	4,700	43,181,250.00	51,187,500.00	812,226,927.75	6.30	**Sufficient**
2024	10,000	91,875,000.00	53,746,875.00	852,838,274.14	6.30	**Insufficient** *Allocated budget for Oral PrEP needs to increase by 70.94% more*
2025	10,000	91,875,000.00	56,434,218.75	895,480,187.84	6.30	**Insufficient** *Allocated budget for Oral PrEP needs to increase by 62.80% more*
2026	10,000	91,875,000.00	59,255,929.69	940,254,197.24	6.30	**Insufficient** *Allocated budget for Oral PrEP needs to increase by 55.05% more*

Table 20. ***(Scenario 2) Budget Needed for Oral PrEP for all Filipinos with substantial risk for HIV VS Projected Budget of the Program for Oral PrEP***

Year	Target number of Oral PrEP users to fund	Total Budget needed to cover the target number of oral PrEP users *(in PHP)*	Projected Budget for oral PrEP *(in PHP)*	Total projected budget of the HIV Program *(in PHP)*	Proportion of oral PrEP budget from the total HIV program budget *(in %)*	INDICATION OF SUFFICIENCY OF BUDGET ALLOCATED FOR ORAL PREP
2022	578,300	5,313,131,250.00	48,750,000.00	773,549,455.00	6.30	**Insufficient** *Allocated budget for Oral PrEP needs to increase by 10,798.73% more*
2023	585,700	5,381,118,750.00	51,187,500.00	812,226,927.75	6.30	**Insufficient** *Allocated budget for Oral PrEP needs to increase by 10,412.56% more*
2024	593,000	5,448,187,500.00	53,746,875.00	852,838,274.14	6.30	**Insufficient** *Allocated budget for Oral PrEP needs to increase by 10,036.75% more*
2025	600,300	5,515,256,250.00	56,434,218.75	895,480,187.84	6.30	**Insufficient** *Allocated budget for Oral PrEP needs to increase by 9,672.89% more*
2026	607,500	5,581,406,250.00	59,255,929.69	940,254,197.24	6.30	**Insufficient** *Allocated budget for Oral PrEP needs to increase by 9,319.15% more*

Household Financial Impact

Evidence not reviewed as the medication costs for the complete course of therapy shall be fully subsidized through the NASPCP. Other costs (e.g., cost of transportation to the facility, cost of workday/hour loss as a result of going to the facility) shall be borne by the user or his/her household. We note that the frequency of visits and distance from the hub may vary the cost of transportation and other costs related to facility visit. These especially become a concern when hubs are not within walking distance and users need to travel before reaching the nearest clinic (UNAIDS, 2020b). Hence, these may further increase direct non-medical and indirect costs by the user.

Recommendation

The **Health Technology Assessment Council (HTAC) recommends the inclusion** of **Oral PrEP (Emtricitabine 200 mg FDC + Tenofovir Disoproxil Fumarate 300 mg)** in the Philippine National Formulary (PNF) to **reduce the risk of acquiring sexually transmitted HIV infection** based on the following evidence:

- **Clinical Efficacy and Safety:**
  - The use of Oral PrEP (in combination with other HIV preventive strategies) compared to placebo or no Oral PrEP shows statistical significance in terms of efficacy for reducing the risk of acquiring HIV infection.
  - The use of Oral PrEP (in combination with other HIV preventive strategies) compared to placebo or no Oral PrEP shows no significant difference in risk in terms of serious adverse events, withdrawal due to adverse events, fracture, any bacterial transmitted infection, syphilis, gonorrhea, herpes simplex virus infection and hepatitis C virus infection. In terms of renal adverse events, results show that oral PrEP was associated with increased risk of renal adverse events compared with placebo or no PrEP. There was an increased risk of gastrointestinal adverse events among users of oral PrEP compared with placebo or no oral PrEP.
  - The use of oral PrEP is safe and efficacious in preventing the transmission of the HIV infection following the 2016 WHO Recommendation with strong recommendation and high certainty of evidence.
- **ELSHI:**
  - There is high acceptability of Oral PrEP among potential users, and its role is being valued as part of national strategy to address HIV/AIDS.
  - Both potential users and implementers agreed that, upon inclusion of oral PrEP to the PNF, social stigma on oral PrEP use (*e.g., censoring of terms related to HIV; perceiving that the use of oral PrEP would supposedly lead to promiscuity; HIV services-related discrimination; poor health-seeking behavior*) may still ensue. Health system and program implementation changes for oral PrEP must be streamlined or scaled up so these societal implications can be addressed. These changes included community mobilization activities (*e.g., participation of members of the community in policy-making and the program cycle for oral PrEP*), multi-population level capacity building for oral PrEP, and oral PrEP streamlining / institutional scaling up, among others.
  - Non-inclusion of oral PrEP for HIV can bind at-risk individuals to the limited number of HIV preventive strategies currently being implemented in the Philippines. Since there are individuals who opt not to use condoms or other existing preventive strategies, the non-inclusion of PrEP can restrict both the general and at-risk individuals from achieving better health outcomes.

- Although there are policy barriers, such as obtaining child assent and access among key populations, there are existing policy enablers for the service delivery of PrEP as well as laws with indirect impact on oral PrEP.

- Potential users and implementers support the need to strengthen health system processes in order to improve access to oral PrEP, not only among key populations, but also among other individuals depending on risks.

- **Cost-effectiveness:**

  While there are studies showing potential value for money on implementing oral PrEP, the results found cannot be directly adopted in the Philippine context and inferred for the Philippine setting on the cost-effectiveness due to differences in the assumed efficacy, cost of oral PrEP, and incidence rate applied in those model settings versus the Philippine setting.

- **Budget Impact:**

  - In terms of cost, including oral PrEP in the Philippine National Formulary for the year 2022 procurement will not incur immediate budget impact to the government, as supplies will have still been donated by the Global Fund prior to this period.

  - It was found to have an anticipated incremental cost of Php 9,264.67 per user in a year (which covers the cost of treatment regimen and monitoring of adverse drug reactions) considering that this will be an add-on to existing HIV preventive strategies (i.e., NPIs).

  - Based on the 5-year costing analysis, while there are observed savings from the treatment of averted HIV infections, the total cost of the intervention arm remains to be more costly considering the cost of oral PrEP:

    - Scenario 1: Target number of users based on enrollment (2,500 to 10,000) - shows that there will be an additional cost of approximately PhP 23,161,675.00 to PhP 290,642,947.69

    - Scenario 2: Projected number of seronegative individuals at substantial risk (578,300 to 607,500) - shows incremental cost of PhP 5,357,758,661.00 to PhP 21,133,946,954.22.

  - If all the seronegative at-risk population are eligible for oral PrEP and the projected budget will be covered by the government, the projected budget for oral PrEP and HIV Program will not be sufficient. Nevertheless, implementing oral PrEP is potentially affordable if the target number of users is based on the enrollment rate of the Program, and if additional available funds are secured by the Program.

Finally, the HTAC recommends that:

1. Program evaluation be put in place to measure the real world effectiveness with the use of Oral PrEP in the local implementation to reduce the risk of sexually acquired HIV-infection;

2. DOH ensures high-quality surveillance following the WHO guidelines to enable the conduct of impact monitoring and assessment;

3. The Program conducts information dissemination on the limitations of PrEP and active campaigns for other STI-preventive strategies;

4. Oral PrEP initiatives be integrated as a part of existing health system processes to reach communities more efficiently; and,

5. The DPCB, through the NASPCP, strengthens the health system domains (e.g., service delivery, interprofessional collaboration, increasing rural/GIDA access to oral PrEP, among others) to ensure a safe and consistent supply, and equitable distribution through all its treatment hubs across the country.

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APPENDIX 1. Critical Appraisal of Chou, et al, 2019

Presented in table 1 is the result of the appraisal for Chou, et al.'s *Evidence Report and Systematic Review for the US Preventive Services Task Force of Preexposure Prophylaxis for the Prevention of HIV Infection*.

Table 1. Critical Appraisal of *Evidence Report and Systematic Review for the US Preventive Services Task Force of Preexposure Prophylaxis for the Prevention of HIV Infection* by Chou et al (2019) using AMSTAR II tool.

Domain	Answer	Remarks from the reviewers
1	Yes	
2*	Partial Yes	No mention of justification for any deviations from the protocol, review not registered prior
3	Yes	
4*	Partial Yes	No mention if searched trial/study registries included/consulted content experts in the field
5	Yes	
6	No	No mention that data extraction was done in duplicate
7*	No	No list of excluded studies that are potentially relevant.
8	Yes	
9*	Partial Yes	No mention of allocation sequence and selection of the reported result from among multiple measurements or analyses of a specified outcome
10	Yes	
11*	Yes	
12	Yes	
13*	No	No discussion was found for the potential impact of bias in the quality of studies
14	Yes	
15*	Yes	
16	Yes	

APPENDIX 2. Oral PrEP ELSHI Report

Link: https://docs.google.com/document/d/1hgsEopfKZbq-nS53qT-OQaTpne9lk6hG/edit