Tenofovir/Lamivudine/Dolutegravir for treatment-naive and treatment-experienced adolescents and adults living with HIV

Service Line	Evidence Summary
Publication Date	09 August 2021
Summary Length	69 Pages
Prepared by	Health Technology Assessment Council Health Technology Assessment Unit
Contact details	hta@doh.gov.ph
Decision of the Secretary of Health	01 September 2021

List of Abbreviations

DOH	Department of Health - Philippines		
EB	Epidemiology Bureau		
NASPCP	National AIDS and STI Prevention and Control Program		
WHO	World Health Organization		
AMSTAR	A MeaSurement Tool to Assess systematic Reviews		
GRADE	Grading of Recommendations Assessment, Development and Evaluation		
PLHIV	People living with human immunodeficiency virus		
RCT	Randomized clinical trials		
Drugs			
NRTI	Nucleoside reverse transcriptase inhibitors		
	TDF Tenofovir	**3TC**	Lamivudine
	FTC Emtricitabine	**AZT**	Zidovudine
	ABC Abacavir		
NNRTI	Non-nucleoside reverse transcriptase inhibitors		
	EFV Efavirenz	**RPV**	Rilpivirine
	NVP Nevirapine		
PI	Protease inhibitors		
	LPV/r Lopinavir/ritonavir	**DRV**	Darunavir
	RTV Ritonavir		
INSTI	Integrase inhibitors		
	DTG Dolutegravir		
TLD	Tenofovir/Lamivudine/Dolutegravir		
TLEfv	Tenofovir/Lamivudine/Efavirenz		

Background

What is HIV?

The human immunodeficiency virus (HIV) is a virus 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 transgender people (TP) (UN AIDS Fact sheet, 2020). HIV, if left untreated, can progress to Acquired Immune Deficiency Syndrome (AIDS).

What are the current interventions for HIV treatment?

International Guidelines

Drug classes for HIV treatment are currently divided into 4: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase inhibitors (INSTIs). In 2016, the WHO published the Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection which recommended that the first-line HIV treatment regimens be composed of 2 NRTI backbone and 1 NNRTI or INSTI. At that time, they recommended Efavirenz (EFV)-based regimen as the preferred regimen for treatment-naive patients. Further, they recommended Dolutegravir (DTG) in combination with NRTI backbone as an alternative regimen. In cases of treatment failure, identified through two (2) consecutive viral load measurements above 1000 copies/mL, 3-6 months apart, with an evaluation for adherence concerns in between tests, the patient is advised to switch to second-line therapy. The recommended second-line treatment is a combination of 2 NRTI backbone and 1 boosted PI or INSTI.

Local Guidelines

In 2018, the DOH issued AO 2018-0024: *Revised policies and guidelines on the use of ART among PLHIV and HIV-exposed infants* which recommends the following treatment regimens (Table 1) for adults and adolescents (≥ 10 y/o) with confirmed positive HIV test

regardless of clinical and immunologic status in the Philippines. These regimens remain as the currently recommended treatment regimens implemented by the NASPCP.

Table 1. Current treatment regimen for treatment-naive and treatment-experienced adolescents and adults living with HIV in the Philippines

Population	Current Treatment Regimens in the Philippines
First-line treatment for ***treatment-naive*** adolescents and adults living with HIV	**Preferred:** Tenofovir (TDF) 300mg + Lamivudine (3TC) 300mg + Efavirenz (EFV) 400-600mg [TLEfv] **Alternative:** Abacavir (ABC) 600mg + Lamivudine (3TC) 300mg + Rilpivirine (RPV)* 25mg **only in asymptomatic patients 12 years old and above, with known CD4 count of > 350 cells/mm3, not pregnant, and not on Rifampicin-containing regimen**
Second-line treatment for ***treatment-experienced*** adolescents and adults living with HIV *These regimens are initiated when the patient is not responding to treatment and has virologic failure. In suspicion of such, patients should be managed in close coordination with a specialist, and blood specimens must be sent to RITM for HIV drug resistance testing before shifting to second-line.*	**Preferred (2 NRTI + LPV/r):** NRTI: ● Zidovudine (AZT) 250-300mg + Lamivudine (3TC) 300 mg *[for those failing TDF or ABC]* ● Tenofovir (TDF) 300mg or Abacavir (ABC) 600mg + Lamivudine (3TC) 300mg *[for those failing AZT]* PI: Lopinavir/ritonavir (LPV/r) 400mg/100mg **Alternative (2 NRTI + DRV + RTV):** NRTI: ● Zidovudine (AZT) 250-300mg + Lamivudine (3TC) 300mg [if previously on TDF or ABC] ● TDF or ABC + 3TC [if previously on AZT] PI: Darunavir (DRV) 800mg + Ritonavir (RTV) 100mg

What are the new proposed treatment regimens?

International Guidelines

In 2018, the WHO issued the *Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendation on early infant diagnosis of HIV* shifting the recommendation to the use of DTG in combination with NRTI backbone from an alternative regimen (in the 2016 WHO guidelines) to the preferred first-line regimen for adults and adolescents (with strong recommendation and moderate-certainty of evidence). This consequently shifted the use of EFV-based regimen from preferred regimen (in the 2016 WHO guidelines) to alternative first-line regimen for the treatment-naive population in the 2018 WHO guidelines. The recommendation was

based on a systematic review by Kanters, et al. entitled, *Systematic literature review and network meta-analysis assessing first-line antiretroviral treatments,* published in the year 2018. For the second-line regimen treatment for treatment-experienced patients, the WHO, in the same updated guidelines, recommended the use of DTG along with 2 NRTI backbone as the preferred second-line regimen for those failing on EFV- and non-DTG-based regimens. This consequently shifted the original 2016 preferred second-line regimen *AZT + 3TC +LPV/r* to an alternative second-line regimen in the current 2018 guidelines. Failing on EFV or virologic failure, in this context, is the same as defined above where viral load is >1000 copies/mL after 2 consecutive tests, 3-6 months apart. This recommendation was based on a 2018 systematic review written by the same set of authors as for the first-line, entitled, *Systematic review: which ART regimen to switch to when failing first-line treatment.*

Further to this, the WHO through FHI 360 in 2019, has recommended that all countries using TLEfv as a first-line regimen, as in the case of the Philippines, should transition to a different combination, which contains dolutegravir (DTG) in place of efavirenz — that is, TLD, with the "D" standing for dolutegravir. This combination therapy is also recommended for use as a second-line regimen for patients failing on efavirenz- or nevirapine-containing regimens or for those failing a non-DTG-containing first-line regimen.

Proposed Treatment Regimen Shift in the Local Guidelines

In light of these global treatment recommendations for PLHIV, the National AIDS and STI Prevention and Control Program (NASPCP) of the DOH-DPCB proposed in the local implementing guidelines for treatment of PLHIV the shift to DTG-based regimens as (1) first line treatment for treatment-naive adolescents and adults living with HIV with TB co-infection; and; as (2) second-line treatment for treatment-experienced adults and adolescents living with HIV, specifically on those failing in TDF-based regimens. Overall, the specific proposed DTG-based regimens to be introduced are as follows:

- As preferred first-line for treatment-naive PLHIV
    - Tenofovir (TDF) 300mg + Lamivudine (3TC) 300mg + Dolutegravir (DTG) 50mg [TLD]
    - *For those with TB co-infection*
        - Tenofovir (TDF) 300mg + Lamivudine (3TC) 300mg + Dolutegravir (DTG) 50mg [TLD]) + Dolutegravir (DTG) 50mg

- As preferred second-line for treatment-experienced PLHIV
    - *For PLHIV with severe ADR to TLEfv; PLHIV failing AZT & ABC-based regimens; PLHIV on NVP-based and RPV-based regimens:*
        - Tenofovir (TDF) 300mg + Lamivudine (3TC) 300mg + Dolutegravir (DTG) 50mg [TLD]
    - *For those* PLHIV failing TDF-based regimens
        - Zidovudine (AZT) 300mg + Lamivudine (3TC) 300mg + Dolutegravir (DTG) 50mg

Of the new proposed regimens above, all drugs, except *DTG (as a single drug preparation)* and *TLD (as fixed dose combination)* are currently listed in the PNF. While these drugs are not yet in the PNF, TLD therapy is currently being implemented by the Program with supplies from the donations of the Global Fund which will end in the year 2022. However, the program can only process the procurement of TLD and DTG, once HTAC provides positive recommendations that will merit their inclusion in the PNF.

To note, the evidence review for *DTG (as a single drug preparation)* is discussed in a separate evidence summary as the indication/ population who will use this single drug in combination with other regimens is different compared to the indication/ population for TLD. This review shall therefore focus on *TLD (as fixed dose combination)* and its use for the following indications:

Table 2. Proposed specific indications for TLD use in adults and adolescents living with HIV in the Philippines *(following the 2018 WHO recommendations)*

Indication/ Population	Proposed Treatment Regimen for TLD
Preferred first-line treatment for ***treatment-naive*** adolescents and adults living with HIV	**Tenofovir (TDF) 300mg + Lamivudine (3TC) 300mg + Dolutegravir (DTG) 50mg [TLD]** *(fixed-dose combination)* Treatment duration: Lifetime treatment
Preferred second-line treatment for ***treatment-experienced*** adolescents and adults living with HIV specifically: *(1) for those who have severe reaction to TLEfv;* *(2) for those failing AZT-based and ABC-based regimens;* *(3) for those on NVP-based or RPV-based regimen*	**Tenofovir (TDF) 300mg + Lamivudine (3TC) 300mg + Dolutegravir (DTG) 50mg [TLD]** *(fixed-dose combination)* Treatment duration: Lifetime treatment

Should TLD be included in the PNF, the proposal is that the recipients of TLD for *treatment-naive patients* shall be for the new cases in 2022. Meanwhile, current treatment-naive patients who are still using the currently implemented treatment regimen TLEfv shall continue to use this therapy until such time that the patients experience severe adverse events; in which case, they will be shifted to TLD.

Description of TLD

Tenofovir/Lamivudine/Dolutegravir (TLD) is a relatively new fixed-dose combination drug that was developed by 2 different innovator companies (WHO, 2018). The drug is a combination of 2 Nucleoside Reverse Transcriptase Inhibitors [NRTIs] (i.e. Tenofovir and Lamivudine) and an integrase inhibitor [INSTI] (i.e. Dolutegravir). According to the fact sheet by the FHI 360 and the USAID, the drug is found to be superior compared to the triple combination of Tenofovir + Lamivudine + Efavirenz in that there was faster suppression of viral load compared to EFV-based regimens, higher drug-resistance barrier compared to NNRTIs, and that being a fixed-dose combination, there is more convenience in taking the drug. The reported potential side effects of the drug include Nausea, diarrhea, headache, agitation, insomnia, and skin rashes. Further, the WHO in July 2019, announced that DTG is safe for women of child-bearing age making TLD the preferred first-line and second-line regimen for pregnant women and women of child-bearing age. In its use with Tuberculosis drugs, the drug level of DTG is reported to be lowered by rifampicin which means that an additional individual DTG tablet should be taken after taking TLD. The WHO Essential Medicines List currently lists TLD for use in managing HIV.

Currently, TLD is not listed in the PNF. However, all other components in the fixed-dose combination (i.e. TDF and 3TC), aside from DTG, are already listed but as single preparations.

Other drugs for HIV in the PNF are as follows:

- ABC
- 3TC
- TDF
    - Tenofovir alafenamide fumarate
    - Tenofovir disoproxil fumarate
- AZT

- EFV
- NVP
- RPV
- TDF/3TC
- TDF/3TC/EFV
- AZT/3TC
- AZT/3TC/NVP
- LPV/r

Following the WHO recommendation and its potential benefit against HIV in the Philippines, this evidence summary shall present the appraisal of evidence for the use of TLD (fixed-dose combination): (1) as the preferred first-line treatment among treatment-naive adults and adolescents living with HIV; (2) as the preferred second-line treatment among treatment-experienced adults and adolescents living with HIV. These shall serve as the evidentiary basis for the recommendation of the listing of TLD (fixed-dose combination) in the PNF.

Policy Question

Should Tenofovir/Lamivudine/Dolutegravir fixed-dose combination be included in the Philippine National Formulary for the management of HIV infection among adults and adolescents?

Research Questions

Clinical effectiveness and safety

1. Among treatment-naïve adolescents and adults living with HIV, how effective is Tenofovir/Lamivudine/Dolutegravir fixed-dose combination as the preferred first-line treatment compared to Tenofovir + Lamivudine + Efavirenz triple therapy in viral suppression and decreasing the incidence of drug resistance?
2. Among treatment-naïve adolescents and adults living with HIV, how safe is Tenofovir/Lamivudine/Dolutegravir fixed-dose combination as the preferred first-line treatment compared to Tenofovir + Lamivudine + Efavirenz triple therapy in reducing the incidence of adverse drug events/ drug reactions and all-cause mortality?

3. Among treatment-experienced adults living with HIV with treatment failure from an EFV-based drug regimen, how effective is Tenofovir/Lamivudine/Dolutegravir fixed-dose combination as the preferred second-line treatment compared to LPV/r-based regimen in viral suppression and decreasing the incidence of drug resistance?
4. Among treatment-experienced adults living with HIV with treatment failure from an EFV-based drug regimen, how safe is Tenofovir/Lamivudine/Dolutegravir fixed-dose combination as the preferred second-line treatment compared to LPV/r-based regimens in reducing the incidence of adverse drug events/ drug reactions and all-cause mortality?

Economic/Budget impact

1. What is the cost-effectiveness of using Tenofovir/Lamivudine/Dolutegravir fixed-dose combination compared to Tenofovir + Lamivudine + Efavirenz as the preferred first-line HIV drug regimen for the treatment-naive patients?
2. What is the cost-effectiveness of using Tenofovir/Lamivudine/Dolutegravir fixed-dose combination compared to LPV/r-based regimen as the preferred second-line HIV drug regimen for the treatment-experienced patients?
3. What is the total medication cost per patient and for the expected number of treatment-naive patients using Tenofovir/Lamivudine/Dolutegravir fixed-dose combination compared to the Tenofovir + Lamivudine + Efavirenz triple therapy for the first year of implementation?
4. What is the total medication cost per patient and for the expected number of treatment-experienced patients switched to Tenofovir/Lamivudine/Dolutegravir fixed-dose combination compared to the currently recommended (i.e. AZT + 3TC + LPV/r) second-line HIV drug regimen for the first year of implementation?
5. What is the total medication cost for the expected number of treatment-naive patients using Tenofovir/Lamivudine/Dolutegravir fixed-dose combination compared to the Tenofovir + Lamivudine + Efavirenz triple therapy for the first 5 years of implementation?
6. What is the total medication cost for the expected number of treatment-experienced patients switched to Tenofovir/Lamivudine/Dolutegravir fixed-dose combination compared to the currently recommended (i.e. AZT + 3TC + LPV/r) for the first 5 years of implementation?

Responsiveness to Disease Magnitude, Severity, and Equity

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 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 increase service coverage have improved HIV-related morbidity and mortality. By the end of 2019, an estimated 81% of people living with HIV knew their status, with 59% achieving suppression of the HIV virus. Additionally, in the year 2019, sixty-eight percent of adults (15 y/o and above) and 53% of children (0-14 y/o) living with HIV globally were receiving lifelong antiretroviral therapy, while 85% of pregnant and breastfeeding women living with HIV also received ART, ensuring the prevention of HIV transmission to newborns (UNAIDS fact sheet, 2020).

HIV in the Philippines

In the Philippines, HIV affects less than 1% of the general population; however, there has been a 203% increase of new HIV infection from 2010 to 2018 (DM 2021-0017). The Philippines experienced the steepest rise in a 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 1 per day in 2008 to 21 per day in 2020. There are a total of 81,169 reported cases of HIV between January 1984 to October 2020. In the month of October 2020 alone, there were a total of 735 confirmed individuals living with HIV, 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: 94% (76,216) are male and more than half (51%, 41,163) are 25-34 years old at the time of diagnosis. Moreover, among the 81,169 cases, the 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).

Presented in table 3 are the local data on the prevalence of PLHIV who have initiated therapy for the years 2016-2019 from the EB of the DOH. From this set of data, we can see that the total number of newly diagnosed PLHIV from 2016 to 2019 was 44,544. Among these, 38,681 PLHIV were initiated on ART, and the average treatment rate for the said years is at 86.2%. Meanwhile, the year-on-year growth percentage on drug initiation was computed to have an average of 19% per year.

Table 3. PLHIV data on newly diagnosed cases from EB for years 2016-2019

	2016	2017	2018	2019	Remarks
Newly diagnosed cases	9,238	11,101	11,427	12,778	44,544 for 4 years
Newly initiated on ART	7,107	9,253	10,519	11,802	38,681 for 4 years (86.8% of the newly diagnosed cases)
Treatment rate	76.93%	83.35%	92.05%	92.36%	Average of 86.2% per year
PLHIV not on treatment	2,131	1,848	908	976	Average of 1,466 per year
y/y growth % on drug initiation		30%	14%	12%	Average of 19% per year

Reference: Epidemiology Bureau (2020)

According to the 2020 TLD/DTG Transition Operational Plan of the NASPCP, the Philippines is seriously committed to ending HIV/AIDS by 2030. As such, they stated that the country adopted the “treat all” policy in 2018 in an effort to close the national treatment gap. The same document mentioned that this led to a significant increase in treatment coverage from 44% to 61%.

HIV drugs in the Philippines are all centrally procured through the NASPCP, and can be accessed only through HIV treatment hubs which include public and private facilities. This has implications on drug access drug access of all treatment-naive and treatment-experienced HIV patients in the Philippines, if this medication will not be included in the PNF. These patients shall end up using their current HIV therapies which limits their potential to experience better improvement in their outcomes, given that this therapy has already been globally recommended on the basis of its better clinical benefit to HIV patients.

Safety and Effectiveness

According to the FDA Philippines, Tenofovir/Lamivudine/Dolutegravir fixed-dose combination tablet has a Monitored-release Certificate of product registration (MR-CPR). 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. Nevertheless, the agency attests, through a letter to the HTAC dated 23 June 2021, that regardless of whether the CPR is an MR or a regular one, the CPR issuance is already an assurance that a drug has undergone a thorough evaluation for safety, quality, and efficacy, albeit newly introduced in the Philippines. Further, the NASPCP has provided international Phase IV trial data to supplement the discussion of evidence on safety and effectiveness.

DTG-based regimen as first-line treatment among treatment-naïve adults and adolescents living with HIV

DESCRIPTION OF AVAILABLE EVIDENCE

This section shall focus on the evidence appraisal of Kanters, et al.'s *Systematic literature review and network meta-analysis assessing first-line antiretroviral treatments*, which was the basis of the 2018 WHO recommendation on the use of Dolutegravir for adolescents and adults living with HIV. This study is an update on a review completed in May 2015, thus, the authors restricted search from Jan 2015 to Feb 2018, and included the 2015 list of included studies in the study. In total, the authors included 90 studies, all of which are randomized clinical trials. The follow-up period of the included studies ranges from 24 to 240 weeks, with a median of 96 weeks.

The included studies in the review had trial participant count ranging from 16 to1857. The trials included are either phases 2, 3, or 4, and the setting of the trials ranges from one country only to worldwide, with more trials done in the United States. The study included dolutegravir-based regimens and other drug regimens such as: DTG + 2NRTI, EFV400 + 2NRTI, Raltegravir (RAL) + 2NRTI, Elvitegravir boosted with cobicistat EVG/c + 2NRTI, Bictegravir (BIC) + 2 NRTI, Doravirine (DOR) + 2NRTI, Rilpivirine (RPV) + 2 NRTI, Nevirapine (NVP) + 2 NRTI, Darunavir boosted with ritonavir (DRV/r) + 2 NRTI, Atazanavir boosted with ritonavir (ATV/r) + 2 NRTI, Lopinavir boosted with ritonavir (LPV/r) + 2 NRTI). On the other hand, the only listed comparator is EFV600 + 2 NRTI.

As for the outcomes in the review, the studies included assessed for viral suppression at 48 and 96 weeks, which were all classified as efficacy outcomes in the research question; as well as mortality, treatment emergent adverse events, and severe adverse events which were all classified as safety outcomes in the research question. Of the two efficacy outcomes of interest, only viral suppression was reported by the study, and drug resistance was not measured. Meanwhile, all the safety outcomes of interest (i.e. incidence of adverse events and mortality) were reported. We note that the authors did not define the outcomes presented except for viral suppression which is set at a threshold value of <50 copies/mL; hence, treatment-emergent and treatment-related adverse events were treated in this assessment as adverse events. The study performed a risk of bias assessment using the instrument endorsed by the Cochrane Collaboration. Quantitative synthesis was performed using network meta-analysis. The reviewers of Kanters et al, 2018 also performed GRADE rating across all outcomes to assess the certainty of evidence.

For the purpose of this assessment, we note that in 2012, the WHO published a study that looked at the possible interchangeability of 3TC and FTC as the two drugs are of similar chemical structure. A systematic review mentioned in the study indicated that the clinical and virological efficacy and safety of the 2 drugs are comparable (WHO, 2012). Hence, in this review, we also considered FTC as a possible combination with TDF and DTG.

We also note that Kanters et al, 2018 did not perform subgroup analysis by specific HIV drug combinations. Hence, we identified which of the included studies in Kanters et al, 2018 used TLD (i.e. DTG + TDF + XTC) and presented the evidence available for these. Upon review of the included trials, there was only one trial (Stellbrink et al, 2013), a phase 2 dose-ranging trial, which assessed DTG + 2 NRTIs (at 10mg, 25mg, and 50mg doses) against EFV + 2 NRTIs among treatment-naive patients living with HIV (n = 205). We note, however, that the proportion of participants who were given the specific TLD combination was not reported, and that the trial did not present specific analysis for patients who received TLD only. The efficacy outcome measures included *proportion of patients with a viral load of <50 copies per mL* and *median CD4+ cell coun*t. On the other hand, the safety outcomes included *adverse events*. There were no reported results for incidence of drug resistance and all-cause mortality.

As such, the assessment team performed additional search for other trials beyond the last search of Kanters et al, 2018 in order to identify specific evidence for TLD. This resulted in the detection of one trial conducted by the NAMSAL ANRS 12313 Study Group with results published in 2019. This is an open-label, multi-center, randomized phase III non-inferiority trial which assessed TLD as the intervention and TLEfv as the comparator among treatment-naive people living with HIV (N = 613). The efficacy outcome measures of the study included the proportion of patients with limited viral suppression (below 50 cp/mL) and the prevalence of drug-resistance mutations. The study also reported discontinuation due to AE/death as a safety outcome as well as other patient-reported outcomes on their quality of life. We then performed a risk of bias assessment using the COCHRANE ROB-2 tool on the primary outcome of NAMSAL Study group, 2019.

As for evidence from Phase IV trials or real-world studies, there are five studies reviewed in this evidence summary which are relevant to our research questions, based on the submission of the proponent (ie., DOH NASPCP):

- Meireles et al 2019 - A retrospective cohort study which used programmatic data among 107,647 treatment-naive adults aged 15-80 years old in Brazil which assessed the effectiveness of TLD versus EFV-based regimens (e.g. TLEfv) and PI-based regimens (e.g. AZT+3TC+LPV/r). Of the 80,584 patients who received EFV-based regimens, 95.53% received TLEfv. The study assessed effectiveness in terms of viral suppression and controlling for other factors such as patient adherence, age, and exposure group, among others.
- Pascom, et al., 2019 - A retrospective cohort study that used programmatic data from the Ministry of Health of Brazil on treatment-naive patients living with HIV aged 12 years old and above. The study had a total of 112,243 patients with 18,830 receiving TLD; 87,896 receiving TLEfv; and 5,517 receiving TDF+3TC+ATV/r. The study assessed the effectiveness of TLD combination in terms of cumulative viraemia - estimated as the area under the viral load curve, calculated using the trapezoidal rule with all available viral load measurements.
- Neesgard et al, 2020 - An ongoing prospective cohort study in 17 European and Australian cohorts (e.g. Denmark, Germany, Sweden, Australia, among others) with available interim results is expected to be finished by 2025. The study assessed virologic and immunologic outcomes of INSTI-based regimen (e.g. TLD) compared to PI/b regimen (e.g. Darunavir, Atazanavir) and NNRTI-based regimen (e.g. TLEfv) among 13,703 participants living with HIV which are either treatment-naive or

treatment experienced. Among the 4,521 ART-naïve participants, 1,914 patients (42.3%) received INSTI-based regimen (e.g. TLD) and 1,359 patients (30.1%) received NNRTI-based regimen (e.g.TLEfv) while the rest received PI/b regimen which is not relevant for this research question. We note, however, that the study did not indicate the proportion of treatment-naive patients who received TLD and TLEfv as the study only provided this information for all participants (i.e, 3,839 patients (79.3%) received TLD among the 4,967 INSTI-based regimen recipients while 946 patients (27.4%) received TLEfv among the 3,454 NNRTI-based regimen recipients). In addition, the study did not present a subgroup analysis for the outcomes of treatment-naive patients who were administered with TLD and TLEfv specifically. The available results in the study used the INSTI-based regimen versus NNRTI-based regimen as a drug class.

- Correa, et al., 2020 - A retrospective cohort study among 222 treatment-naive patients living with HIV aged 18 years or older in Brazil. The study assessed the effectiveness and safety of the introduction of DTG-based regimens (i.e. 99.1% received TLD and 0.9% received DTG + ABC + 3TC) to the said group of patients, and compared these results with the established baseline, in terms of virologic response (viral load of <50 cp/mL) and incidence of adverse events.
- Chilambe, et al., 2019 - A pharmacovigilance study with a descriptive cross-sectional design. The study reviewed 45 spontaneous case reports concerning DTG-containing adverse drug events (ADEs) submitted by health workers to the Zambia Medicines Regulatory Authority in Zambia. The study looked at suspected ADEs experienced by patients taking DTG-based antiretroviral regimen. We note that the population for this study was not stratified if they are treatment-naive or treatment-experienced. Further, the proportion of patients who took TLD was also not mentioned and there was no available subgroup analyses for this specific drug.

KEY FINDINGS FROM AVAILABLE EVIDENCE

Evidence from Phase II-III trials

Kanters et al, 2018

Efficacy Outcomes

Table 4. Key findings on the efficacy of DTG-based regimen vs EFV-based for treatment-naive adolescents and adults living with HIV as presented by Kanters, et al., 2018

Outcome	Results			Overall quality of evidence	Is DTG-based regimen better?
	Pairwise Odds ratio	NMA Odds ratio	Absolute effects		
Efficacy Outcome 1: ***Viral suppression***					
Viral suppression at 48 wks	1.79 (1.25 to 2.58)	1.86 (95% CrI: 1.44-2.40)	74 per 1000 (47 to 98)	High	Yes DTG was statistically significantly more effective than standard dose EFV in achieving viral suppression at 48 weeks, based on 53 trials
Viral suppression at 96 wks	1.65 (1.21 to 2.24)	1.93 (95% CrI: 1.52-2.47)	94 per 1000 (63 to 121)	High	Yes DTG was statistically significantly more effective than standard dose EFV in achieving viral suppression at 96 weeks, based on 28 trials
Viral suppression at 144 wks	1.44 (1.08 to 1.92)	1.44 (95% CrI: 1.08-1.92)	39 per 1000 (11 to 83)	Low	Yes DTG was statistically significantly more effective than standard dose EFV in achieving viral suppression at 144 weeks , based on 6 trials It is important to note that for this outcome, there was low quality of evidence owing to the low number of events, imprecise estimates,

					and some concerns on risk of bias

Viral suppression: viral load that is less than 50 cp/mL

Safety outcomes

Table 5. GRADE table of safety outcomes for treatment-naive adolescents and adults living with HIV as presented by Kanters, et al., 2018

Outcome	Results			Overall quality of evidence	Is DTG-based regimen better?
	Pairwise Odds ratio	NMA Odds ratio	Absolute effects		
Safety outcome 1: **Mortality**	0.20 (0.01 to 4.16)	0.64 (95% CrI 0.09-4.87)	-4 per 1000 (-12 to 9)	Low	• Not statistically significant, based on 29 trials • Authors note the trials were underpowered for this, citing many comparisons with 0 events which renders estimates unreliable.
Safety outcome 2: **Treatment-related serious adverse events** *Note: the authors did not define what they meant by 'serious adverse events'*	0.22 (0.05 to 1.03)	9.79 (95% CrI: 0.02-507.24)	126 per 1000 (-12 to 822)	Very low	• No significant difference, based on 129 trials • With only 81 treatment-related serious adverse events across the evidence base, there were too few events to obtain reliable estimates. Results of the analysis nonetheless are still presented
Safety outcome 3: **Treatment-related adverse events** *Note: the*	0.38 (0.29 to 0.50)	0.33 (95% CrI: 0.25-0.44)	-215 per 1000 (-256 to -170)	Moderate	• Yes, there is statistically significantly less treatment-related adverse events in the DTG-based group compared to EFV-based group,

authors did not define what they meant by adverse events					based on 59 trials ● The authors noted that while none of the treatments were distinguishable with respect to treatment emergent adverse events, both DTG and EFV400 had lower odds of leading to a treatment-related adverse event compared to standard dose EFV (i.e. 600 mg qd).

Viral suppression: viral load that is less than 50 cp/mL

Critical Appraisal of Kanters et al, 2018

Following the algorithm of the appraisal tool, the review has an overall rating of critically low quality of evidence. The study incurred more than one critical flaw such as no mention that the study only included low risk of bias RCTs and no mention of tests for publication bias, and multiple non-critical weaknesses such as no mention of protocol registration, no justification for publication restrictions, no report on sources of funding, no sensitivity analyses shown and no declaration of conflict of interest.

It is important to note, however, that the appraisal tool used was originally meant for appraising systematic reviews and not network-meta analyses. This tool was opted to be used by the assessment team for the lack of an alternative tool specific for appraising network meta-analyses.

Despite the evidence having a rating of critically low quality of evidence, the Subcommittee on Drugs deems that the review is still useful in assessing Dolutegravir; these flaws do not crucially negate or contradict the evidence for clinical efficacy and safety. In addition, the 2018 WHO's *Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendation on early infant diagnosis of HIV* said that recommendations made on DTG-based regimens on the said guidelines were formulated following WHO standards for guideline development and based on up-to-date systematic reviews of the evidence,

complemented with additional information regarding values and preferences, feasibility and acceptability and cost.

Stellbrink et al, 2013

From Kanters, et al., we identified one trial authored by Stellbrink, et al. (2013) which used the combination of different doses of DTG + 2 NRTIs (i.e. TDF+FTC, ABC+3TC) compared to EFV600 added with the same set of 2 NRTIs, and assessed several outcomes to measure its efficacy and safety among people living with HIV (N=205).

In terms of efficacy, the results favor the intervention where there was higher CD4+ cell count compared to the comparator. However, the result for the proportion of patients with a viral load of <50 copies/mL is inconclusive. There was no analysis for drug resistance. In terms of safety, the direction of results is indiscernible as: there was no difference in any adverse events (AE); there was a small difference in serious AEs; and, any drug-related AE only happened in a small proportion of participants. There was no analysis for all-cause mortality.

NAMSAL ANRS 12313 Study Group, 2019

This Phase III trial used the combination of DTG + TDF + 3TC compared to EFV400 + TDF + 3TC , and assessed several outcomes to measure its efficacy and safety among people living with HIV (N=613). We note that in the absence of a reported summary statistic, the Assessment Team performed an independent calculation for all outcomes except for the proportion of patients with viral load <50 cp/mL at week 48, and the proportions of patients with at least mild depression, mild anxiety, and mild stress.

Efficacy Outcomes

Overall, in terms of efficacy, the primary endpoint shows that TLD is non-inferior with low-dose EFV400 + TDF + 3TC in terms of viral suppression. The study reported a slightly higher baseline change in the CD4+ T-cell in the TLD group albeit insignificant.

Table 6. Efficacy outcomes reported by NAMSAL ANRS 12313 Study Group, 2019

Outcome	DTG Group (N=310)	EFV400 Group (N=303)	Summary statistic	Authors' Interpretation

Proportion of patients with viral load < 50 cp/mL at week 48 *(Viral suppression)*	231 (74.5%)	209 (69.0%)	Difference of the proportions between 2 groups: 5.5 percentage points (95% CI: -1.6 to 12.7) ***(reported by the authors)***	The difference meets the criterion for noninferiority (margin of -10%) (P<0.001) but not for superiority (P = 0.13)
Median change from baseline in the CD4+ T-cell at week 48	178 per cubic millimeter	150 per cubic millimeter	Difference: 28 per cubic millimeter ***(calculated by the assessment team)***	Not significantly greater in the dolutegravir group than in the EFV400 group *NOTE: The assessment team notes that the results for both groups are not clinically significant as CD4+ T-cell counts are < 200 per cubic mm, the threshold used as one of the criteria by the US CDC in defining AIDS (Li, et al., 2021)*

Safety Outcomes

Overall, in terms of safety, the all-cause mortality or the incidence of discontinuation due to adverse events or death is comparable between the two groups. There was no analysis for the incidence of adverse drug events alone.

Table 7. Safety outcomes reported by NAMSAL ANRS 12313 Study Group, 2019

Outcome	DTG Group (N=310)	EFV400 Group (N=303)	Summary statistic	Authors' Interpretation
Discontinuation due to AE/death	6 (1.9%)	7 (2.3%)	Difference: -0.37 percentage points ***(calculated by the assessment team)***	No death was found to be directly linked to either treatment. Causes of death of the patients were detailed for all except in one patient in the DTG group with unknown circumstances.

Humanistic Outcomes

Overall, in terms of humanistic or patient-related outcomes, the quality of life is comparable between the two groups. The authors used the Short Form 12 (SF-12) health survey questionnaire to assess these outcomes. The domains of the said form are divided into 8 domains that assess physical and mental health. The Physical health-related domains include General Health (GH), Physical Functioning (PF), Role Physical (RP), and Body Pain (BP). On the other hand, the Mental health-related domains include Vitality (VT), Social Functioning (SF), Role Emotional (RE), and Mental Health (MH).

Based on the results, no significant differences were found between the two groups on most outcomes except for the mental component where the TLD group had a lower score than the EFV400+TDF+3TC group at week 48.

Table 8. Humanistic outcomes reported by NAMSAL ANRS 12313 Study Group, 2019

Outcome	DTG Group (N=310)	EFV400 Group (N=303)	Summary statistic	Authors' Interpretation
Proportion of patients with at least mild depression	8.0%	9.7%	Difference: -1.7 percentage points (95% CI: -2.9 to 6.3) ***(reported by the authors)***	There were no significant differences between the two groups with regard to the following outcomes: the proportion of participants who had depression, anxiety, or stress over time
Proportion of patients with at least mild anxiety	12.9%	9.7%	Difference: 3.18 percentage points (95% CI: -3 to 4.5) ***(reported by the authors)***	
Proportion of patients with at least mild stress	1.7%	1.8%	Difference: -0.06 percentage points (95% CI: -1.9 to 8.3) ***(reported by the authors)***	
Mean Physical component of HR-QOL at week 48	53.2	53.3	Difference: -0.11 ***(calculated by the assessment team)*** *p = 0.80* ***(reported by the authors)***	Mean scores on the SF-12 physical and mental component summaries at baseline and over time did not differ significantly between the two groups,

Mean Mental component of HR-QOL at week 48	45.3	46.6	Difference: -1.33 ***(calculated by the assessment team)*** *p = 0.03* ***(reported by the authors)***	except at week 48, when the mean score on the mental component summary was significantly lower in the dolutegravir group than in the EFV400 group

Critical Appraisal of NAMSAL ANRS 12313 Study Group, 2019

Based on our assessment, the overall risk of bias of the study is low. Although the study was open-label, randomization procedures were performed. All protocol deviations have been documented and likely to have not affected the primary outcome of the study. The knowledge of the participants on the intervention does not also change the measurement of the viral load since it is laboratory-based. The results of the risk of bias assessment is provided in Appendix 2.

Evidence from Phase IV trials/ Real-world studies

All three studies (Mereiles, et al., 2019, Pascom, et al., 2019, and Neesgaard, et al., 2020) have consistently shown the significant clinical benefit of TLD vs TLEfv among treatment-naive patients living with HIV in real-world settings. In terms of safety, Correa, et al. found that after the introduction of ART in patients aged 18 years or older, there was a 10.4% incidence of adverse events, which include gastrointestinal symptoms, neuropsychiatric symptoms, and systemic symptoms. This is aligned with the results of Chilambe, et al., which noted the same group of adverse events.

For outcomes reported by Neesgard et al (2020), multivariable logistic regression showed that the INSTI-based regimens (group with TLD) were comparable to NNRTI-based regimens in terms of composite treatment outcomes and on-treatment analysis, but were significantly superior in terms of ≥25% CD4 increase in count from baseline and ≥750 CD4 cells/μL. Further, we note that the protocol of this study mentions several safety outcomes but the results of those are not yet published in the interim results as the trial is still ongoing. Below are their key findings:

Table 9. Outcomes reported by the included phase 4 trials/real-world studies

Outcomes	Results	Interpretation

Mereiles et al, 2019		
Viral suppression at 12 months	TLEfv (N=76 986): 84.0% TLD (N=11 262): 90.5% Univariate OR: 1.82 (95% CI: 1.70–1.94) Adjusted OR: 1.56 (95% CI: 1.40–1.75)	Viral suppression by 12 months was 84.0% [95% CI 83.7–84.2] with TLE and 90.5% (95% CI 90.0–91.0) with TLD. In the multivariable intent-to-treat-analogous analysis, controlling for cofactors related to viral suppression including adherence, the adjusted odds ratio for TLD's viral suppression relative to TLE was 1.56 (95% CI 1.40–1.75), which significantly favors TLD. Findings were robust to secondary per-protocol analogous and sensitivity analysis.
Pascom et al, 2019		
Cumulative viraemia (area under the viral load curve calculated using the trapezoidal rule)	Univariate analysis: TLD: mean area of 689.53 log_{10} copy-days/mL TLEfv: mean area of 728.03 log_{10} copy-days/mL TDF+3TC+ATV/r: mean area of 743.90 log_{10} copy-days/mL	Univariate analyses showed that **cumulative viraemia was significantly lower in patients receiving TLD** as compared with those receiving TLEfv and TDF+3TC+ATV/r (p<0.0001) for both pairwise comparisons
Neesgard, et al (ongoing with interim results)		
cTO <200 cp/mL (Composite Treatment Outcome was defined success as viral load (VL) <200 copies/mL and failure as at least one of: VL ≥ 200 copies/mL, unknown VL in the time window, any changes of antiretroviral therapy (ART) regimen, AIDS, or death)	aOR: 0.94 (95% CI: 0.79-1.11)	Compared to INSTIs (group with TLD), the adjusted odds ratio (aOR) of cTO success was similar.
On-treatment analysis <200 cp/mL (Including only individuals with known VL and no regimen changes was performed)	aOR: 0.73 (95% CI: 0.38-1.14)	Compared to INSTIs (group with TLD), the adjusted odds ratio (aOR) of on-treatment analysis <200 cp/mL was similar.
≥25% CD4 increase in count from baseline	aOR: 0.75 (95% CI: 0.59-0.95)	The adjusted odds ratio (aOR) **significantly favors** INSTI (group with

		TLD).
≥750 CD4 cells/μL	aOR: 0.60 (95% CI: 0.47-0.77)	The adjusted odds ratio (aOR) of ≥25% CD4 increase in count **significantly favors** INSTI (group with TLD).
Correa, et al., 2020		
Viral response at 24 weeks (viral load < 50 cp/mL)	After ART introduction: 89.1% (95% CI: 83%-93.5%)	The estimated incidence of virologic response by week 24 of treatment was 89.1% (95% CI: 83% to 93.5%). The median viral load of patients at the beginning of ART was 334,000 copies. After 24 weeks, the median viral load decreased to 193 copies.
Incidence of adverse event	After ART introduction: 23/222 (10.4%; 95% CI: 7%-15.2%)	The frequency of adverse events following the ART introduction was 10.4%. Most of those who used this regimen and reported adverse events only reported one single complaint (43.5%), while 34.8% reported at least two complaints and 21.7% three or more complaints. The types of complaints include gastrointestinal symptoms (e.g. diarrhea, nausea, vomiting), neuropsychiatric symptoms (e.g. insomnia, dizziness), and systemic symptoms (e.g. fever, skin blemishes).
Chilambe, et al., 2019		
Frequency of adverse drug events, by category	After using DTG-based regimen: ● Neurological and neuropsychiatric - 30% ● Altered sense of balance - 16.7% ● General symptoms - 16.7% ● Gastrointestinal effects - 13.3% ● Neuropathy - 11.7% ● Hypersensitivity - 5.0% ● Musculoskeletal - 3.3% ● Cardiovascular effects - 1.7% ● Sexual dysfunction - 1.7%	Among the reported ADEs, neurological and neuropsychiatric symptoms were the most frequently experienced. According to the study, neuropsychiatric effects include dizziness, drowsiness, insomnia, confusion, loss of memory, agitation, hallucination, delusions, depression, abnormal dreams and impaired concentration lasting a few weeks or months. Fisher's exact test reveals that age and sex was significantly associated with all of the ADEs reported. Neurological symptoms were largely experienced by patients above 50 years old.

DTG-based regimen as second-line treatment among treatment-experienced adults and adolescents living with HIV

DESCRIPTION OF AVAILABLE EVIDENCE

This section shall focus on the evidence appraisal of Kanters, et al.'s *Systematic review: which ART regimen to switch to when failing first-line treatment*, which was the basis of the 2018 WHO recommendation on the use of Dolutegravir for treatment-experienced adults and adolescents.

This study is an update on a review completed in May 2015, thus, the authors restricted the search from Jan 2015 to Feb 2018, and included the 2015 list of included studies in the study. In total, the authors included 9 studies, all of which are randomized clinical trials. The follow-up period of the included studies ranges from 48 to 144 weeks. The included studies in the review had trial participant counts ranging from 200 to1286. The trials included are either phases 3 or 4, and the setting of the trials ranges from one country only to worldwide, with more trials done in the African and South American continent. The study included dolutegravir-based regimens and other regimens such as: DTG + optimized 2NRTI, LPV/r + RAL, RAL + optimized 2NRTI, DRV/r + optimized 2NRTI. On the other hand, the listed comparators are LPV/r + 2NRTI and ATV/r + optimized 2NRTI.

As for the outcomes measured and reported in the review, the studies included assessed for viral suppression at 24, 48, and 96 weeks which were classified as efficacy outcomes in the research question; as well as mortality, treatment-emergent and treatment-related adverse events, which were classified as safety outcomes in the research question. Of the two efficacy outcomes of interest, only viral suppression was reported by the study, and drug resistance was not measured. Meanwhile, all the safety outcomes of interest (i.e. incidence of adverse events and mortality) were reported. We note that the authors did not define the outcomes presented except for viral suppression which is set at a threshold value of <50 copies/mL; hence, treatment-emergent and treatment-related adverse events were treated in this assessment as adverse events. The study performed a risk of bias assessment using the instrument endorsed by the Cochrane Collaboration. Quantitative synthesis was performed using network meta analysis. The assessment team also performed a GRADE rating across all outcomes to assess the certainty of evidence.

For the purpose of this assessment, we note that in 2012, the WHO published a study that looked at the possible interchangeability of 3TC and FTC as the two drugs are of similar chemical structure. In the study, it was mentioned that a systematic review indicated that the clinical and virological efficacy and safety of the 2 drugs are comparable. Hence, in this review, we also considered FTC as a possible combination with TDF and DTG.

We note that Kanters et al, 2018 did not perform subgroup analysis by specific HIV drug combinations. Hence, we identified which of the included studies in Kanters et al, 2018 used TLD (i.e. DTG + TDF + XTC) and presented the evidence available for these. Upon review of the included trials, there was only one trial (Aboud et al, 2019), an open-label, non-inferiority, phase 3b trial, which assessed DTG + 2 NRTIs against LPV/r-based regimens. However, only 41% participants in the trial also received other DTG-based therapies (vs 100% of our comparator of interest), and the trial did not present specific analysis for patients who received TLD only. The efficacy outcome measures of the study included viral suppression - defined as having a viral load of <50 copies per mL - at 24 and 48 weeks, proportion of patients with less than 400 cp/mL at 24 and 48 weeks, CD4+ cell count at 24 and 48 weeks, time to viral suppression, among others. The safety outcome measures, on the other hand, included incidence of adverse events. The study did not report the following outcomes of interest in our assessment: incidence of drug resistance and all-cause mortality.

As such, the assessment team performed additional search for other trials beyond the last search of Kanters et al, 2018 in order to identify specific evidence for TLD. However, no trials were detected from the search that compares TLD with the comparator of interest, i.e. LPV/r-based regimens, for second-line treatment.

From the review of Kanters et. al., 2018, the assessment team performed a critical appraisal of their systematic review using the Assessment of Multiple Systematic Review (AMSTAR) 2 Tool. Presented in the next sections are the reported efficacy and safety (i.e. odds ratio and the overall quality of evidence per outcome), as well as the results of the critical appraisal of Kanters et. al., 2018.

As for evidence from Phase IV trials or real-world studies, there are two studies reviewed in this evidence summary which are relevant to our research questions, based on the submission of the proponent (DOH-NASPCP):

- Umar, et al., 2021 - A prospective cohort study in Nigeria that involved treatment-experienced patients living with HIV aged 18 to 60 years old (N=286 patients). The study assessed the effectiveness of transitioning to TLD in terms of viral suppression (viral load < 50 cp/mL) and health-related quality of life; the results were compared to the baseline characteristics. We note that this study currently only has a preprint version.
- Chilambe, et al., 2019 - A pharmacovigilance study with a descriptive cross-sectional design. The study reviewed 45 spontaneous case reports concerning DTG-containing adverse drug events (ADEs) submitted by health workers to the Zambia Medicines Regulatory Authority in Zambia. The study looked at suspected ADEs experienced by patients taking DTG-based antiretroviral regimen. We note that the population for this study was not stratified if they are treatment-naive or treatment-experienced. Further, the proportion of patients who took TLD was also not mentioned and there was no available subgroup analyses for this specific drug.

KEY FINDINGS FROM AVAILABLE EVIDENCE

Evidence from Phase II-III trials

Kanters et al, 2018

Efficacy outcomes

Table 10. GRADE table of efficacy outcomes for treatment-experienced adults living with HIV as presented by Kanters, et al., 2018 for DTG + 2NRTIs vs LPV/r + 2NRTIs

Outcome	Results			Overall quality of evidence	Is the DTG-based regimen better?
	Pairwise Odds ratio	NMA Odds ratio	Absolute effects		
Viral suppression at 24 wks	2.11 (1.45 to 3.07)	2.11 (95% CI: 1.45-3.07)	151 per 1000 (78 to 216)	High	Yes, based on 2 trials DTG-based regimen was associated with a statistically significantly higher proportion of patients achieving viral suppression with an odds ratio of 2.11 (95% CI: 1.45 to 3.07)

					relative to LPV/r + 2 NRTIs
Viral suppression at 48 wks	2.11 (1.40 to 3.19	2.11 (95% CI: 1.40-3.21)	109 per 1000 (54 to 154)	Moderate	Yes, based on 6 trials DTG was associated with a statistically significantly higher proportion of patients achieving viral suppression compared to all other treatment options, with the exception of ATV/r + 2 NRTIs.

Viral suppression: viral load that is less than 50 cp/mL

Safety outcomes

Table 11. GRADE table of safety outcomes for treatment-experienced adults living with HIV as presented by Kanters, et al., 2018 for DTG + 2NRTIs vs LPV/r + 2NRTIs

Outcome	Results			Overall quality of evidence	Is DTG-based regimen better?
	Pairwise Odds ratio	NMA Odds ratio	Absolute effects		
Mortality	0.33 (0.03 to 3.16)	0.26 (95% CI: 0.01-2.19)	-12 per 1000 (-23 to 18)	Very low	No statistically significant difference There were only 143 deaths across 6 trials
Treatment-related serious adverse events	0.99 (0.14 to 7.05)	0.94 (95% CI: 0.10-6.73)	1 per 1000 (-44 to 20)	Very low	No statistically significant difference, based on 2 trials
Treatment-related adverse events	0.31 (0.21 to 0.45)	0.31 (95% CI: 0.21-0.45)	-47 per 1000 (-66 to -31)	Low	Yes, there is statistically significantly less treatment-related adverse events in the DTG-based group compared to

					EFV-based group, based on 4 trials DTG + 2 NRTIs was associated with fewer patients experiencing a treatment-related adverse event compared to all treatments in the network with the exception of LPV/r

Viral suppression: viral load that is less than 50 cp/mL

Critical Appraisal of Kanters et al, 2018

Following the algorithm of the appraisal tool, the review has an overall rating of critically low quality of evidence. The study incurred more than one critical flaw such as no mention that the study only included low risk of bias RCTs and no mention of tests for publication bias, and multiple non-critical weaknesses such as no mention of protocol registration, no justification for publication restrictions, no report on sources of funding, no sensitivity analyses shown and no declaration of conflict of interest.

It is important to note however, that the appraisal tool used was originally meant for appraising systematic reviews and not network-meta analyses. This tool was opted to be used by the assessment team for the lack of an alternative tool specific for appraising network meta-analyses.

Despite the evidence having a rating of critically low quality of evidence, the Subcommittee on Drugs deems that the review is still useful in assessing Dolutegravir; these flaws do not crucially negate or contradict the evidence for clinical efficacy and safety. In addition, the 2018 WHO's *Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendation on early infant diagnosis of HIV* said that recommendations made on DTG-based regimens on the said guidelines were formulated following WHO standards for guideline development and based on up-to-date systematic reviews of the evidence, complemented with additional information regarding values and preferences, feasibility and acceptability and cost.

Aboud, et al., 2019

From Kanters, et al., we identified one trial authored by Aboud, et al. (2019), a open-label, multinational, multicentre, parallel-group, non-inferiority, randomised, active controlled, phase 3b trial, which used the combination of DTG + 2 NRTIs (i.e. AZT+3TC, TDF+3TC, TDF+FTC, ABC+3TC) compared to LPV/r added with the same set of 2 NRTIs, and assessed several outcomes to measure its efficacy and safety among people living with HIV (N=627). We note that while the evidence presented by Aboud et al. included the drug of interest (i.e. TLD) and the comparator of interest (i.e. LPV/r-based regimens), the reported results are composed of values combined from the different components of the intervention group - not TLD alone. The population that took the TLD as the intervention is 41% of the total population under the intervention group. In contrast, the population that took the LPV/r-based under the comparator group is 100%.

Efficacy Outcomes

In summary, viral suppression at 24 and 48 weeks of the DTG + 2 NRTIs combination was noninferior to the LPV/r-based regimens. Since noninferiority was established, the authors also analyzed if the viral suppression at week 48 for the DTG combination was superior to the LPV/r combination. In their analysis, they found out that the former was superior to the latter ($p < 0.0001$). There was no analysis presented for the incidence of drug resistance.

Table 12. Efficacy outcome measures reported by Aboud, et al., 2019, that is relevant to the research question

Outcome	DTG Group (N=155)	LPV/r Group (N=50)	Summary statistic reported by the study	Authors' Interpretation
Viral suppression at week 24	257/312 (82%)	215/312 (69%)	Adjusted treatment difference : 13.8% (95% CI: 7.3-20.3)	With an adjusted treatment difference of 13.8% (95% CI: 7.3-20.3), there was a significantly greater proportion (p<0.0001) of participants who achieved viral suppression in the intervention group compared with the comparator group at week 24

Viral suppression at week 48	261/312 (84%)	219/312 (70%)	Adjusted treatment difference: 13.8% (95% CI: 7.3-20.3)	With an adjusted treatment difference of 13.8% (95% CI: 7.3-20.3), there was a significantly greater proportion (p<0.0001) of participants who achieved viral suppression in the intervention group compared with the comparator group at week 48

Viral suppression: viral load that is less than 50 cp/mL

Safety Outcomes

The study looked at adverse events which were analyzed as incidence of AEs, treatment-related AEs, and treatment-related SAEs. The analyses show that the incidence of adverse events for the DTG + 2 NRTIs was generally less than the LPV/r + 2 NRTIs group. Summary statistics were calculated by the assessment team as the authors were not able to present a comparison. There was no analysis for all-cause mortality in the study.

Table 13. Safety outcome measures reported by Aboud, et al., 2019, that is relevant to the research question

Outcome	DTG Group (N=155)	LPV/r Group (N=50)	Summary statistic calculated by the assessment team	Authors' Interpretation
Incidence of adverse events	223/314 (71%)	244/310 (79%)	Difference (calculated by assessment team): 8% (95% CI: 1.20-14.70)	The safety profile of the intervention group was generally more favorable than the comparator group
Treatment-related adverse events (Any grade)	50/314 (16%)	119/310 (38%)	Difference (calculated by assessment team): 22% (95% CI: 15.13-28.61)	There were more treatment-related adverse events in the comparator group than the intervention group
Treatment-related serious adverse events	3/314 (1%)	2/310 (1%)	no difference	The number of treatment-related serious adverse events were similar across treatment groups

Evidence from Phase IV trials/ Real World Studies

In terms of effectiveness, Umar et al. found that after switching to TLD, there is a significant improvement in achieving viral suppression - defined as having a viral load of <50 copies/mL. In terms of safety, Chilambe et al. noted the following adverse events: gastrointestinal symptoms, neuropsychiatric symptoms, and systemic symptoms, among others. In terms of quality of life, Umar et al demonstrated that there is a statistically significant improvement in overall health-related quality of life after patients transition to TLD. Below are their key findings:

Table 14. Outcomes reported by the included phase 4 trials/real-world studies

Outcomes	Results	Interpretation
Umar, et al., 2021 (preprint)		
Viral suppression (at < 50 cp/mL)	Baseline: 121 (46.4%) had viral suppression After switching to TLD: 209 (80.1%) had viral suppression	There was a statistically significant improvement after switching to TLD (p<0.001)
Overall Health-related quality of life	Baseline: mean score of 72.72 +- 7.75 After switching to TLD: mean score of 88.22+-8.43	There was a statistically significant improvement in overall HRQoL after switching to TLD (all domains having p-value<0.001, except sexual function having p=0.015)
Chilambe, et al., 2019		
Frequency of adverse drug events, by category	After using DTG-based regimen: ● Neurological and neuropsychiatric - 30% ● Altered sense of balance - 16.7% ● General symptoms - 16.7% ● Gastrointestinal effects - 13.3% ● Neuropathy - 11.7% ● Hypersensitivity - 5.0% ● Musculoskeletal - 3.3% ● Cardiovascular effects - 1.7% ● Sexual dysfunction - 1.7%	Among the reported ADEs, neurological and neuropsychiatric symptoms were the most frequently experienced. According to the study, neuropsychiatric effects include dizziness, drowsiness, insomnia, confusion, loss of memory, agitation, hallucination, delusions, depression, abnormal dreams and impaired concentration lasting a few weeks or months. Fisher's exact test reveals that age and sex was significantly associated with all of the ADEs reported. Neurological symptoms were largely experienced by patients above 50 years old.

WHO statement on the clinical evidence of TLD

The WHO, on its briefing note entitled, *Dolutegravir (DTG) and the fixed dose combination (FDC) of tenofovir/lamivudine/dolutegravir (TLD)*, published April 2018, said that the TLD was originally developed by 2 different innovator companies. For this reason, there have been few studies published with this specific combination, as drug companies rarely sponsor trials that use products from competitors. However, while there have been scarce studies, the WHO also mentions that there have also been abundance of clinical evidence for the three components of the TLD (i.e. TDF, 3TC, DTG). Thus, the WHO considers that there is sufficient clinical data for this triple combination.

Furthermore, in the same note, as mentioned in the clinical effectiveness and safety section of this evidence summary, Lamivudine and Emtricitabine are considered interchangeable, doubling the already abundant clinical evidence as the basis for efficacy and safety of TLD.

Household Financial Impact

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 patient or his/her household. We note that the frequency of visits and distance from the treatment hub may vary the cost of transportation and other patient costs related to facility visit. These especially become a concern when treatment hubs are not within walking distance and patients need to travel before reaching the nearest clinic (UNAIDS, 2020). Moreover, most hubs are located in major cities and may not be accessible to PLHIVs in rural areas or islands where no hubs exist. (Gangcuangco, 2019) Hence, these may further increase direct-non medical and indirect costs by the patient. However, it is likely that these transportation costs are not significantly different compared to current standard of care, which also requires daily oral maintenance medications.

Cost-effectiveness

According to WHO's *Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendation on early infant diagnosis of HIV*

published in 2018, DTG offers substantial potential cost savings, especially in low- and middle-income countries. The median prices of generic DTG-containing and EFV-containing fixed-dose formulations are comparable (US$ 75–80 per person per year), but with economies of scale it is expected that the price of DTG could be US$ 17–21 per person per year, lower than the current first-line regimen prices. A review of 12 studies assessing the cost–effectiveness, cost utility or cost savings of DTG as first-line ART for adults concluded that DTG-based regimens are highly cost-effective compared with the standard of care.

None of the models, however, evaluated the potential effects of neural tube defects (NTD) with DTG exposure at conception and potential exclusion of women and adolescent girls of childbearing potential from the population to receive DTG-based regimens. To note, incidence of NTD in newborn babies of women taking DTG at time of conception is at 0.3% (95% CI: 0.13-0.69%) compared with 0.10% (95% CI: 0.06-0.17%) for any non-DTG ART (Chouchana, et al., 2020). This reference was published in the The Lancet in 2020 looking at the reporting of NTD cases in the WHO pharmacovigilance database, a database that receives reports from more than 150 countries, for DTG compared to EFV and other ARTs (e.g. Abacavir [ABC], Emtricitabine [FTC], Lopinavir [LPV]). In the article, Chouchana, et al reports that the odds ratio of NTD in DTG compared to EFV is 10.4 (95% CI: 4.9-21.7) and the odds ratio for NTD in DTG when compared to other ARTs is 6.4 (95% CI: 3.7-10.9) while in EFV compared to other ARTs is 0.4 (95% Ci: 0.2-0.7). The authors of the correspondence however, noted that all the cases of NTD for DTG were reported after the broadcast of the safety signal in May 2018. This could reflect a notoriety bias for DTG after the communication which could have resulted in the inflation of the odds ratio of reporting for DTG-related cases of NTD. Gauging its impact in the local setting, we note that only 5.1% (2,931 /60,411 cases) of PLHIVs in the last five years are female, of which 15.3% (449/2,931cases) are reported pregnant based on the HIV/AIDS & ART Registry of the Philippines.

Of these 12 economic evaluation studies, two (2) [Phillips, et al. (2017) and Zheng, et al. (2018)] were on LMICs.

- **Phillips et al, (2017)** assessed the cost-effectiveness of public health policy options in the presence of pretreatment NNRTI in sub-saharan Africa. It is a cost-utility analysis which compared the costs and benefits of different treatment policy options for both treatment-naive and treatment-experienced PLHIV [i.e. (1) no change in policy - giving EFV-containing as first-line regimen for ART initiators (e.g. TLEfv) ; (2) for antiretroviral therapy (ART) initiators with prior antiretroviral exposure, introduce

resistance test at treatment initiation and use of dolutegravir if NNRTI resistance is detected; (3) for all ART initiators, introduce resistance test at treatment initiation and use dolutegravir if NNRTI resistance is detected; (4) for ART initiators with previous antiretroviral drug exposure, introduce dolutegravir as first-line regimen; and (5) for all ART initiators, introduce dolutegravir-containing as first-line regimen (e.g. TLD)] using the HIV Synthesis Model, an individual-based simulation model on HIV transmission, progression, and response to ART, through a healthcare payer perspective, applying a 3% discount rate for both costs and outcomes per year, and a time horizon of 20 years.

Health opportunity costs were captured by converting the costs to the health care system into health losses using the cost-effectiveness threshold (i.e. USD 500 per DALY averted). For each policy option, the study computed for net DALY, which is calculated as the sum of DALYs plus the ratio of costs to the cost-effectiveness threshold. Then, they calculated for the difference in Net DALY (i.e. incremental DALY) so they can determine if the 4 new new ART options (i.e. options 2-5 where in option 5 is the introduction of DTG-containing [e.g. TLD] regimen) are cost-effective compared to no ART policy change (e.g. using TLEfv). The policy option with lowest Net DALY will be considered as the cost-effective option.

Based on their analysis, option (5), an option to transition all ART initiation from EFV-containing (i.e. TLEfv) first-line regimen to DTG-containing regimen (e.g. TLD) is predicted to be cost-effective (i.e. incremental Net DALYs of -50,669) in low-income settings in Sub-Saharan Africa, at any level of NNRTI drug resistance. Other options' Net DALYs are: Option (2) -2,857; Option (3) -22,249; and Option (4) -9,190. The cost can be much lower if the DTG-based regimen to be used is the fixed-dose combination (i.e. Tenofovir/Lamivudine/Dolutegravir). The analyses in the study also showed that in cases of high prevalence of NNRTI drug resistance, postponing the transition to DTG-containing regimens results in a negative effect on population health, increasing the urgency of transitioning from EFV-containing regimen. Sensitivity analysis results show that the worst case scenario for DTG-containing regimen (i.e. higher viral load rebound than in base case, higher risk for inflammatory syndrome for people with low CD4 count than those in EFV-containing regimen, inflammatory syndrome causes hospitalization and associated with a 5% mortality risk, higher risk for drug-related birth defect than those in EFV-containing regimen, and a 5-fold increase in the rate of drug stock-outs for the 1st year of DTG

implementation) has little effect on the conclusion of using DTG for all ART initiators. The study did not perform Budget impact analysis. Overall, the study concludes that using DTG as first-line regimen for all those who will be starting in ART is cost-effective in low-income settings. This policy becomes more urgent in places with high prevalence of NNRTI drug resistance.

- **Zheng, et al. (2018)** was a cost-effectiveness analysis using microsimulation model, which compared the clinical and economic performance of TDF/3TC + DTG, compared to TDF/3TC/EFV (TLEfv fixed-dose combination) among treatment-naive patients in India. The model was performed through a lifetime horizon, using a health systems perspective, applying a 3% discount rate for both costs and outcomes per year. In their model, patients are started on either the intervention or comparator as first-line therapy. Those who will be failing will then proceed to second-line ART of a PI-based regimen (e.g. LPV/r-based regimen). The benefits as a result of taking TDF/3TC + DTG vs TLEfv are measured in the study in terms of years of life saved, proportion of people alive, proportion of people remaining on first-line ART, number of HIV infection transmissions averted. Meanwhile for costs, the study measured for both cumulative ART and non-ART costs of HIV care. The study used a cost-effectiveness threshold of USD 800 per year of life saved (YLS).

  Based on their analysis, compared to the TLEfv, the TDF/3TC + DTG strategy was cost effective for treatment-naive PLHIV in India, with an ICER of USD 130.00/YLS. The study also conducted a multi-way sensitivity analysis where they considered different drug formulations available for each combination of the comparator and intervention. With a three drug regimen, the DTG-based strategy was shown to be cost-effective compared to the three drug regimen of the EFV-based strategy. When the cost for second-line ART was varied, the DTG-based strategy still remained cost-effective when compared to the EFV-based. Budget impact analyses for three-drug regimen of the intervention and comparator showed cost-savings for 2-year and 5-year timeframe. Overall, the study concludes that DTG-based strategy substantially improves overall survival, increases life expectancy, and is likely to be cost-effective - potentially even cost-saving. The cost incurred by the DTG-based regimen may be substantially lower in the presence of a fixed-dose combination.

Further, in a recent cost-utility analysis using microsimulation model by Belay, et al., 2021, the study compared the cost-effectiveness of TLD with TLEFv among treatment-naive patients in Ethiopia, from a healthcare payer perspective. The model was performed through

a lifetime horizon, using a healthcare payer perspective, applying a 3% discount rate for both costs and outcomes per year. The study used a cost-effectiveness threshold up to three times the GDP of Ethiopia (i.e.USD 951.10 GDP per capita). The benefits as a result of taking TDF/3TC + DTG vs TLEfv are measured in the study in terms of quality-adjusted life months. The study did not mention whether productivity losses and gains are considered in the model. Meanwhile, cost implications considered were lifetime costs. In the model, patients are started on either TLD or TLEfv as first-line therapy. Based on treatment response or adverse drug effects (ADEs), those who will be failing will then shift to the other regimen. Similar to the models from the WHO review, the study did not consider neural tube defects associated with DTG. Based on their analysis, TLD is cost-effective compared to TLE for treatment-naive patients in Ethiopia with an ICER of USD 13.33 per QALY gained. An alternative scenario where the time horizon is only until 5 years showed dominance for TLD with cost savings of USD 1.00 per patient and an expected 0.17 QALY gain. The ICER value computed for the base-case analysis (i.e., lifetime horizon), although cost-incurring, is observed to be far below the recommended threshold. Budget impact analysis was not performed by the study. Sensitivity analysis results showed that the probability of ADEs, treatment response or price of both regimens, and utility value of different health states were found to be influential parameters. Overall, the study concludes that DTG-based first-line regimen appears to be a cost-effective strategy to treat adult HIV patients in Ethiopia.

Overall, the cited economic evals in low-middle income settings have concluded that TLD compared to TLEfv demonstrated value for money for treatment-naive (Phillips, 2017; Zheng, 2018; Belay, 2021) and treatment-experienced (Phillips, 2017) PLHIV. We note however that none of these studies have incorporated that associated high risk for NTD as a result of using DTG. Future economic evaluations are anticipated to address this research gap.

Affordability & Viability

This section presents the 1-year comparative costing and 5-year budget impact of using TLD among (1) treatment-naive patients and (2) treatment-experienced patients. The cost analysis only included direct medical costs consisting of the cost of medication and of human resource, which were identified as cost implications cited by the DPCB in their submission.

For the unit costs, the cost of a one month supply of TLD is PHP 549.00 (cost per bottle) and DTG having PHP 263.00 (cost per bottle), as cited in the 2021 Annual procurement plan of the DOH. On the other hand, the cost for a one month supply of TLEfv is also PHP549.00 (cost per bottle), and the cost of one month of supply of the LPV/r + AZT/3TC combination for second-line is PHP 2,084.23 (cost per bottle), as cited in the same reference. The dosing per day of all the included drugs (i.e. TLD, DTG, and TLEfv - 1 tablet a day, LPV/r - 4 tablets a day, and AZT/3TC - 2 tablets a day) was based on the 2018 WHO treatment guideline for HIV. The same guidelines also state that lifetime treatment would be needed for HIV. Meanwhile, the cost for the human resource was borne by the DPCB, as cited in their Philippine Health Sector HIV Strategic Plan for years 2020-2022, hence was included in the analysis. This consists of fees for professionals in treatment hubs which include physicians, nurses, pharmacists, social workers, case managers, data managers, and administrative personnel. This cost was computed by dividing the average salary of the professionals by the number of patients seen every month and was expressed as cost per patient in the reference which already incorporates the costs of compensation of all cited professionals.

In summary, based on the costing analysis that will be presented in the succeeding subsections, the use of TLD among the treatment-naive PLHIV versus the cost of TLEfv will incur comparable direct costs.

For the treatment-experienced users, the use of TLD therapy will result in a 5-year cost savings of PHP 1.86 billion compared to the current therapy since there is an apparent medication cost difference between TLD and AZT + 3TC + LPV/r due difference in unit cost as the latter is taken multiple times a day (i.e. LPV/r 2 tablets twice a day and AZT/3TC one tablet twice a day).

Costing for TLD use among Treatment-Naive Patients

As for TLD use as first-line treatment among treatment-naive patients, users consist of newly diagnosed people living with HIV. TLD therapy among treatment-naive patients consists of taking one tablet per day of the TLD fixed-dose combination. While there are PLHIV with tuberculosis who will use TLD, we excluded them in this calculation and will include it in a separate assessment for the DTG single preparation. Hence, the calculation for treatment-naive patients will purely be PLHIV without tuberculosis. We then compared TLD to TLEfv, the currently recommended preferred combination for first-line treatment for treatment-naive.

As for the scenario that will simulate the cost of covering all target users for TLD among treatment-naive patients, the computed 1-year cost per patient was multiplied to the newly diagnosed cases which were provided by the DPCB and the DOH-EB.

The total medication cost of TLD therapy in one year for treatment-naive patients amounts to PHP 6,588.00. Including professional fees, the total cost amounts to PHP 11,193.00. Similarly, the total medication cost of using TLEfv therapy is also PHP 6,588.00 in one year. Hence, there is no cost difference for the entire annual target users, as the costing inputs for TLD have the same costs as the TLEfv. Additional costing details are reflected in the Appendix.

Table 15. Comparative costing for treatment-naive adolescents and adults living with HIV for the 1st year of implementation

Parameter	Intervention (TLD)	Comparator (TLEfv)	Remarks
Cost of medicine (per month)	PHP 549.00	PHP 549.00	price per bottle good for 1 month source: DPCB (based on 2021 procurement plan)
Number of dosage units per day	1	1	Daily dosage regimen source: 2018 WHO HIV Treatment guidelines
Duration of treatment	12	12	in months, lifetime treatment source: 2018 HIV WHO treatment guidelines
Drug regimen cost per patient per year	PHP 6,588.00	PHP 6,588.00	-
Other medical costs associated with the use of the drug	PHP 4,605.00	PHP 4,605.00	professional fees of health professionals in treatment hubs source: DPCB (based on Philippine health sector HIV strategic plan 2020-2022)
Total treatment cost per patient per year	PHP 11,193.00	PHP 11,193.00	-
Expected number of patients who will use the drug	17,370	17,370	New patients initiated on ART source: patients initiated on treatment

			from EB
Estimated cost for all users for Year 1	**PHP 194,423,334.01**	**PHP 194,423,334.01**	
INCREMENTAL COST (PHP)	**PHP 0.00**		**No Budget Difference**

As for the 5-year comparative costing, we used the same costing inputs for the calculation of the per patient level costing and multiplied this number with the estimated target users per year. The number of users in the succeeding years were calculated based on the computed average annual growth rate of 19% estimated from the yearly cases of drug initiation and the existing cases from the previous year for the years 2016-2019 provided by the Epidemiology Bureau of the DOH, presented in table 3. Our calculation did not include percentage of users failing treatment and switching out from the treatment, as well as mortality rate and rate of lost-to-follow-up.

.

Using these inputs, the total incremental cost, which was the difference between the costs of the intervention and the comparator, of covering TLD for 5 years for all the estimated treatment-naive PLHIV would be zero, as presented in table 18.

Table 16. 5-year comparative drug costing for treatment-naive adolescents and adults living with HIV

Year	Total patients	Calculation without discounting			Calculation with discounting		
		Cost of TLD (PHP)	Cost of TLEfv (PHP)	Incremental Cost (PHP)	Cost of TLD (PHP)	Cost of TLEfv (PHP)	Incremental Cost (PHP)
Y1	17,370	PHP 194,423,334.01	PHP 194,423,334.01	**PHP 0.00**	-	-	**-**
Y2	38,464	PHP 430,522,492.05	PHP 430,522,492.05	**PHP 0.00**	PHP 376,035,017.94	PHP 376,035,017.94	**PHP 0.00**
Y3	63,999	PHP 716,336,195.17	PHP 716,336,195.17	**PHP 0.00**	PHP 584,743,715.25	PHP 584,743,715.25	**PHP 0.00**
Y4	94,828	PHP 1,061,408,694.70	PHP 1,061,408,694.70	**PHP 0.00**	PHP 809,743,611.21	PHP 809,743,611.21	**PHP 0.00**
Y5	131,967	PHP 1,477,106,172.52	PHP 1,477,106,172.52	**PHP 0.00**	PHP 1,053,156,286.64	PHP 1,053,156,286.64	**PHP 0.00**
TOTAL	346,627	PHP 3,879,796,888.44	PHP 3,879,796,888.44	**PHP 0.00**	PHP 2,823,678,631.05	PHP 2,823,678,631.05	**PHP 0.00**

Costing for TLD use among Treatment-Experienced Patients

As for TLD use as second-line treatment among treatment-experienced patients, as per DPCB, users consist of those who have severe reaction to TDF-based regimen, those failing AZT & ABC-based regimens, and those on NVP-based and RPV-based regimens. TLD therapy among treatment-experienced patients consists of taking one tablet per day of the TLD fixed-dose combination while the therapy with LPV/r + AZT/3TC consists of taking 4 tablets per day of LPV/r and 2 tablets per day of the AZT/3TC fixed dose combination. We then compared TLD to the currently recommended preferred combination for second-line treatment for treatment-experienced, LPV/r + AZT/3TC .

As for the scenario that will simulate the cost of covering all target users for TLD among treatment-experienced patients for year 1, the annual cost per patient was multiplied to the total number of users of TLD, which was composed of the number of patients who had severe adverse events for EFV, number of patients who failed in AZT- and ABC-based regimens, and number of patients who failed in NVP- and RPV-based regimen.

Considering this input, the total cost of TLD therapy in year 1 alone for all treatment-experienced patients amounts to PHP 6,588.00. Meanwhile, the estimated budget impact to cover for the same timeframe and number of patients using the LPV/r-based regimen is PHP 25,010.76. There is a budget difference of PHP 152,466,761.76 for the entire annual target users for the first year of implementation. In addition, we note that those failing in NVP and RPV-based regimens were only accounted for the first year since that will be the last year of its procurement. The main driver for the cost in this calculation is the fact that the comparator is taken multiple times a day (i.e. LPV/r 2 tablets twice a day and AZT/3TC one tablet twice a day). Additional costing details are reflected in the Appendix.

Table 17. Comparative costing for treatment-experienced adolescents and adults living with HIV for the 1st year of implementation

Parameter	Intervention (TLD)	Comparator (AZT + 3TC + LPV/r)	Remarks
Cost of medicine (per month)	PHP 549.00	PHP 2084.23	per bottle (good for 1 month) Source: 2021 annual procurement plan
Number of dosage units per day	1	2 (for AZT/3TC) 4 (LPV/r)	Daily dosage regimen source: 2018 WHO HIV Treatment guidelines

Duration of treatment (months)	12	12	in months, lifetime treatment source: DPCB
Treatment cost per patient per year	PHP 6,588.00	PHP 25,010.76	-
Other medical costs associated with the use of the drug	PHP 4,605.00	PHP 4,605.00	professional fees of health professionals in treatment hubs source: NASPCP (based on Philippine health sector HIV strategic plan 2020-2022)
Total treatment cost per patient per year	PHP 11,193.00	PHP 29,615.76	-
Expected number of patients who will use the drug	8,276	8,276	Based on data on those having severe ADR to EFV and those failing AZT- and ABC-based regimen Source: DPCB
Estimated cost for all users **for Year 1**	**PHP 92,633,268.00**	**PHP 245,100,029.76**	
INCREMENTAL COST (PHP)	**- PHP152,466,761.76**		**Cost savings of PHP 152M**

As for the 5-year comparative costing, we used the same costing inputs for the calculation of the per patient level costing and multiplied this number with the estimated target users per year. The number of users in the first year were provided by DPCB based on their scale-up plan for 2022. For the succeeding years, the number of projected users for the next year came from Clinton Health Access Initiative (CHAI) Tool for ARV Forecasting while the projection for the last year were computed by the assessment team. We assumed a 2.78% growth rate for PLHIV with severe adverse drug reactions and a -0.49% growth rate for those who are failing AZT-based and ABC-based regimens. Calculation did not include percentage of users failing treatment and switching out from the treatment, as well as mortality rate and rate of lost-to-follow-up.

Using these inputs, the cost savings from year 1 to year 5 is PHP 152,466,761.76 to PHP 596,524,878.66. Overall, the total cost savings of covering TLD for 5 years for all the estimated treatment-experienced PLHIV would be PHP 1,858,041,018.43.

Table 18. 5-year comparative drug costing for treatment-experienced adults living with HIV

Year	Patients transitioned to TLD as 2nd line	Calculation without discounting			Calculation with discounting		
		Cost of TLD (PHP)	**Cost of LPV/r + AZT/3TC (PHP)**	**Incremental Cost (PHP)**	**Cost of TLD (PHP)**	**Cost of LPV/r + AZT/3TC (PHP)**	**Incremental Cost (PHP)**
Y1	8,276	PHP 92,633,268.00	PHP 245,100,029.76	**-PHP 152,466,761.76**	-	-	**-**
Y2	14,069	PHP 157,474,317.00	PHP 416,664,127.44	**-PHP 259,189,810.44**	PHP 137,544,167.18	PHP 363,930,585.59	**-PHP 226,386,418.41**
Y3	20,014	PHP 224,021,373.05	PHP 592,742,179.85	**-PHP 368,720,806.80**	PHP 182,868,171.20	PHP 483,854,182.96	**-PHP 300,986,011.76**
Y4	26,117	PHP 292,322,439.70	PHP 773,461,200.47	**-PHP 481,138,760.77**	PHP 223,011,389.62	PHP 590,069,846.54	**-PHP 367,058,456.92**
Y5	32,380	PHP 362,426,854.98	PHP 958,951,733.64	**-PHP 596,524,878.66**	PHP 258,405,338.67	PHP 683,719,332.88	**-PHP 425,313,994.20**
TOTAL	100,856	**PHP 1,128,878,252.73**	**PHP 2,986,919,271.16**	**-PHP 1,858,041,018.43**	**PHP 801,829,066.67**	**PHP 2,121,573,947.97**	**-PHP 1,319,744,881.29**

Recommendation

The HTAC recommends the **inclusion of Tenofovir/Lamivudine/Dolutegravir (TLD) in the Philippine National Formulary (PNF)** for the **first-line treatment** of HIV among treatment-naive adolescents and adults living with HIV, due to the following reasons:

- The use of TLD compared to EFV-based regimens shows **statistical significance in terms of efficacy for achieving viral suppression** at 48 and 96 weeks based on high quality of evidence.
- The use of TLD compared to standard dose EFV-based regimens shows **lower odds for treatment-related adverse events**, based on moderate quality of evidence. No statistical differences were found for odds for mortality and treatment-related serious adverse events, based on very low to low quality of evidence.
- In terms of cost, our projection shows that there is no additional cost for the government in using TLD versus TLEfv for treatment-naive PLHIV.

In addition, the HTAC recommends Tenofovir/Lamivudine/Dolutegravir (TLD) for the **second-line treatment** of HIV among treatment-experienced adults living with HIV, due to the following reasons:

- The use of TLD compared to LPV/r-based regimens shows **statistical significance in terms of efficacy for achieving viral suppression at 24 and 48 weeks** based on moderate to high quality of evidence.
- The use of TLD compared to LPV/r-based regimens shows **lower odds for treatment-related adverse events**, based on low quality of evidence. No statistical differences were found for odds for mortality and treatment-related serious adverse events, based on very low quality of evidence.
- In addition, shifting to once-daily dosing of the fixed-dose combination TLD may improve patient adherence compared with the current regimen *LPV/r + AZT/3TC* consisting of separate drugs required to be taken multiple times a day *(i.e, LPV/r - 2 tablets twice a day and AZT/3TC - 1 tablet twice a day)*.
- In terms of cost, the 5-year comparative drug costing calculation shows annual cost-savings for the government in using TLD versus LPV/r-based regimen ranging from PHP 152M to PHP 596M.

Lastly, including TLD in the PNF shall enable nationwide access to fully subsidized, safe, and effective therapies for treatment-naive and treatment-experienced PLHIV in the Philippines.

To optimize access to this therapy, the DPCB, through the NASPCP, must ensure consistent supply and equitable distribution through all its treatment hubs across the country.

References

1. AIDS/HIV: Department of Health website. (n.d.). Retrieved March 5, 2021, from https://doh.gov.ph/faqs/aids-hiv

2. Belay, Y. B., Ali, E. E., Chung, K. Y., Gebretekle, G. B., & Sander, B. (2021). Cost-Utility Analysis of Dolutegravir- Versus Efavirenz-Based Regimens as a First-Line Treatment in Adult HIV/AIDS Patients in Ethiopia. PharmacoEconomics - Open 2021, 1–10. https://doi.org/10.1007/S41669-021-00275-6

3. Correa, A., Monteiro, P., Calixto, F., d'Arc Lyra Batista, J., de Alencar Ximenes, R. A., & Montarroyos, U. R. (2020). Dolutegravir: Virologic response and tolerability of initial antiretroviral regimens for adults living with HIV. PLoS ONE, 15(8 August 2020), 1–10. https://doi.org/10.1371/journal.pone.0238052

4. Danjuma Umar, Umar Ndagi, Bala Waziri, Shafiu Mohammed, Ndagi Usman, H. A.-M. F. (2019). Impact of Tenofovir / Lamivudine / Dolutegravir (Tld) on the Health-Related Quality of Life and Clinical Outcomes of HIV / AIDS Patients at a Tertiary Health Facility in Niger State. Research Square, 1–18.

5. Department of Health-Philippines (2021) Department Memo 2021-0017: Interim Guidelines on the Pre-exposure prophylaxis for the prevention of HIV in the Philippines.

6. Department of Health-Philippines (n.d.) PHILIPPINES ADDRESSES RISING TREND IN NEW HIV INFECTIONS: Department of Health website. Retrieved March 8, 2021, from https://doh.gov.ph/node/10649#:~:text=A UNAIDS Report on the,an estimated 10,500 in 2016.&text=Majority of the new infections,year old MSM and TGW.

7. Department of Health-Philippines (2020) PNAC observes World AIDS Day Philippines 2020: Department of Health website. Retrieved March 8, 2021, from https://doh.gov.ph/press-release/PNAC-observes-World-AIDS-Day-Philippines-2020#:~:text=According to the DOH HIV,704) of whom were male.

8. Department of Health-Philippines. (2018) Administrative Order 2018-0024: Revised Policies and Guidelines on the Use ofAntiretroviral Therapy (ART) among People living with Human immunodeficiency virus (HIV) and HIV—exposed infants. (2018).

9. Drugs.com. (n.d.). Dolutegravir (Professional Patient Advice) Retrieved March 10, 2021, from https://www.drugs.com/ppa/dolutegravir.html

10. Kanters, S., Jansen, J., Zoratti, M., Forrest, J., Humphries, B., & Campbell, J. (2018). Systematic literature review and network meta-analysis assessing first-line ART treatments in : Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant d. World Health Organization.

11. Kanters, S., Jansen, J., Zoratti, M., Forrest, J., Humphries, B., & Campbell, J. (2018). Systematic review: which ART regimen to switch to when failing first/line treatment: updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of. World Health Organization.

12. Li, R., Duffee, D., & Gbadamosi-Akindele, M. F. (2021). CD4 Count. Handbook of Disease Burdens and Quality of Life Measures, 4164–4164. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK470231/

13. HIV.gov (2021, March 02). Pre-Exposure Prophylaxis. Retrieved March 8, 2021, from https://www.hiv.gov/hiv-basics/hiv-prevention/using-hiv-medication-to-reduce-risk/pre-exposure-prophylaxis

14. Max, B., & Vibhakar, S. (2014). Dolutegravir: A New HIV Integrase Inhibitor: Pharmacokinetics. Retrieved March 10, 2021, from: https://www.medscape.com/viewarticle/836804%0Ahttp://www.medscape.com/viewarticle/836804_3

15. Meireles, M. V., Pascom, A. R. P., Duarte, E. C., & McFarland, W. (2019). Comparative effectiveness of first-line antiretroviral therapy: Results from a large real-world cohort after the implementation of dolutegravir. Aids, 33(10), 1663–1668. https://doi.org/10.1097/QAD.0000000000002254

16. NAMSAL ANRS 12313 Study Group. (2019). Dolutegravir-based or low-dose efavirenz–based regimen for the treatment of HIV-1. New England Journal of Medicine, 381(9), 816-826.

17. National Institute of Health (2020) HIV Treatment: The Basics. Retrieved March 8, 2021, from https://hivinfo.nih.gov/understanding-hiv/fact-sheets/hiv-treatment-basics

18. Neesgaard, B., Mocroft, A., Zangerle, R., Wit, F., Lampe, F., Günthard, H. F., … Lundgren, J. (2020). Virologic and immunologic outcomes of treatment with integrase inhibitors in a real-world setting: The RESPOND cohort consortium. PLoS ONE, 15(12 December), 1–19. https://doi.org/10.1371/journal.pone.0243625

19. Phillips, A. N., Cambiano, V., Nakagawa, F., Revill, P., Jordan, M. R., Hallett, T. B., … Africa, W. G. on M. P. R. to H. L. of P.-A. D. R. in S.-S. (2018). Cost-effectiveness of public-health policy options in the presence of pretreatment NNRTI drug resistance in sub-Saharan Africa: a modelling study. The Lancet. HIV, 5(3), e146. https://doi.org/10.1016/S2352-3018(17)30190-X

20. UN AIDS (2020) Global HIV & AIDS statistics - 2020 fact sheet. Retrieved March 8, 2021, from https://www.unaids.org/en/resources/fact-sheet

21. World Health Organization. (2013). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. (June). Retrieved from https://www.who.int/hiv/pub/guidelines/arv2013/download/en/

22. World Health Organization. (2016). The Use of Antiretroviral Drugs for treating And Preventing HIV infection guidelines HIV/AIDS Programme. Retrieved from http://apps.who.int/iris/bitstream/10665/85322/1/WHO_HIV_2013.7_eng.pdf

23. World Health Organization. (2019). Update of Recommendations on First-and Second-Line Antiretroviral Regimens. In WHO Guidelines. Retrieved from http://apps.who.int/bookorders.

24. World Health Organization. (2019). eEML - Electronic Essential Medicines List. Retrieved March 10, 2021, from 27 February 2020 website: https://list.essentialmeds.org/?section=323&indication=346&year=&age=&sex=

25. World Health Organization (2020) HIV/AIDS. Retrieved March 8, 2021, from https://www.who.int/news-room/fact-sheets/detail/hiv-aids

26. Zheng, A., Kumarasamy, N., Huang, M., Paltiel, A. D., Mayer, K. H., Rewari, B. B., … Freedberg, K. A. (2018). The cost-effectiveness and budgetary impact of a dolutegravir-based regimen as first-line treatment of HIV infection in India. Journal of the International AIDS Society, 21(3). https://doi.org/10.1002/JIA2.25085

Appendix 1. Critical Appraisal of Kanters, et al., 2018

Originally, there are 7 critical domains; however, upon discussion of the HTAC subcommittee on Drugs, it was decided to exclude domain 2, a question on if the study protocol was registered prior to its implementation, reducing the critical domains to 6. Presented in table 1A is the result of the appraisal for Kanters, et al.'s *Systematic literature review and network meta-analysis assessing first-line antiretroviral treatments*, while presented in table 1B is the result of the appraisal for Kanters, et al.'s Systematic review: which ART regimen to switch to when failing first-line treatment.

Table 1A. Critical Appraisal of *Systematic literature review and network meta-analysis assessing first-line antiretroviral treatments* by Kanters, et al., 2018 using AMSTAR II tool.

Domain	Answer	Remarks from the assessment team
1	Yes	
2	No	No mention of protocol registration
3	Yes	
4*	Partial Yes	No justification for publication restrictions
5	Yes	
6	Yes	
7*	Yes	
8	Yes	
9*	Yes	
10	No	Did not report sources of funding
11*	Yes	
12	No	No sensitivity analysis shown
13*	No	Did not explicitly show that the study only included low risk-of-bias RCTs
14	Yes	
15*	No	No mention of tests for publication bias
16	No	No declaration of conflict of interest

Table 1B. Critical Appraisal of S*ystematic review: which ART regimen to switch to when failing first-line treatment* by Kanters, et al., 2018 using AMSTAR II tool.

Domain	Answer	Remarks from the assessment team
1	Yes	
2	No	No mention of protocol registration
3	Yes	
4*	Partial Yes	No justification for publication restrictions
5	Yes	
6	Yes	
7*	Yes	
8	Yes	
9*	Yes	
10	No	Did not report sources of funding
11*	Yes	
12	No	No sensitivity analysis shown
13*	Yes	
14	Yes	
15*	No	No mention of tests for publication bias
16	No	No declaration of conflict of interest

Appendix 2. Risk of Bias Analysis of the Viral Suppression outcome of NAMSAL ANRS 12313 Study Group, 2019

Study details

Reference	NAMSAL ANRS 12313 Study Group. (2019). Dolutegravir-based or low-dose efavirenz–based regimen for the treatment of HIV-1. New England Journal of Medicine, 381(9), 816-826.

Study design

X Individually-randomized parallel-group trial

☐ Cluster-randomized parallel-group trial

☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental:	TLD	Comparator:	TLEfv

Specify which outcome is being assessed for risk of bias	Proportion of patients with viral load < 50 cp/mL at week 48
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Treatment difference: 5.5% [95% CI: -1.6 to 12.7] *Page 6 of research paper*

Is the review team's aim for this result…?

to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions

☐ failures in implementing the intervention that could have affected the outcome

☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

Journal article(s) with results of the trial

Trial protocol

Statistical analysis plan (SAP)

☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)

☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)

☐ "Grey literature" (e.g. unpublished thesis)

☐ Conference abstract(s) about the trial

☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)

☐ Research ethics application

☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)

☐ Personal communication with trialist

☐ Personal communication with the sponsor

Risk of bias assessment

Responses <u>underlined in green</u> are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	"Randomization was stratified according to baseline viral load (<100,000 copies per milliliter vs. ≥100,000 copies per milliliter) and trial site. Participants were randomly assigned, in a 1:1 ratio, to receive dolutegravir or EFV400 in a central procedure performed before the start of the trial (Table S2 in the Supplementary Appendix)." *Research paper, Page 3* "Subjects may be randomized as soon as all pre-inclusion assessments and HIV-1 RNA measurement are completed and the results are available and documented. Once all the information necessary to assess the eligibility of the subject is available, the investigator verifies all the inclusion and noninclusion criteria and sends the inclusion form with the ID number to the person in charge of the randomization. A treatment arm is then assigned to the patient." "On inclusion, the pharmacy concerned will receive the randomisation record and will be able to dispense the assigned treatment" *Protocol, page 25 and 30*	Y / PY / PN / N / NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y / PY / PN / N / NI
1.3 Did baseline differences between intervention groups	"Participants were randomly assigned, in a 1:1 ratio, to receive dolutegravir or EFV400 in a central	Y / PY / PN / N / NI

suggest a problem with the randomization process?	procedure performed before the start of the trial (Table S2 in the Supplementary Appendix)." *Research paper, page 3*	
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	**Comments**	**Response options**
2.1. Were participants aware of their assigned intervention during the trial?	*Open-label trial*	Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI

2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	Table S4. Summary of Protocol Deviations Leading to Exclusion From the Per-Protocol Population Through Week 48	NA / Y / PY / PN / N / NI
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA / Y / PY / PN / N / NI
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	The primary analysis examined the difference between treatment groups in the proportion of participants with a viral load of less than 50 copies per milliliter at week 48, which was to be first tested for noninferiority in the intention-to-treat and per-protocol populations and then tested for superiority at a two-sided significance level of 0.05 if noninferiority was shown (Table S2 in the Supplementary Appendix). The noninferiority of dolutegravir to EFV400 could be concluded if the lower limit of the two-sided 95% confidence interval for the difference between the two groups in the proportion of participants with a viral load of less than 50 copies per milliliter was above −10 percentage points. This margin was chosen for its consistency across other trials and European and FDA recommendations.	Y / PY / PN / N / NI

	Research paper, page 3	
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	**Comments**	**Response options**
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	17 out of 310 participants in the DTG group and 23 out of 303 participants in the EFV group did not have the outcome due to death, lost of follow up, withdrawal or missing viral load in the window. Table S6.	Y / PY / PN / N / NI

	Table S6	
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	The percentage of the missing outcome is 5.48% for the TLD group while it is 7.5% for the TLE group.	NA / Y / PY / PN / N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	**Comments**	**Response options**
4.1 Was the method of measuring the outcome inappropriate?	"All data will be collected on a paper Case Report Form (CRF). A CRF will be completed for all patients and signed by the investigator. The CRF will be checked for accuracy,	Y / PY / PN / N / NI

	authenticity and completeness of the data and will be stored in a safe place accessible only to authorized persons. Data collected on the CRF will be entered in an electronic database specifically designed for the study. The design of the database will be associated with the design of the CRF for a better optimization" *Protocol, page 45*	
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	An external quality control will be performed for 10% of the viral load tests and genotypic resistance tests in the laboratory of virology, UMI 233, IRD, Montpellier. *Protocol, page 46*	Y / PY / PN / N / NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Open-label study	NA / Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	An external quality control will be performed for 10% of the viral load tests and genotypic resistance tests in the laboratory of virology, UMI 233, IRD, Montpellier. *Protocol, page 46*	NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	**Comments**	**Response options**
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	The primary analysis examined the difference between treatment groups in the proportion of participants with a viral load of less than 50 copies per milliliter at week 48, which was to be first tested for noninferiority in the intention-to-treat and per-protocol populations and then tested for superiority at a two-sided significance level of 0.05 if noninferiority was shown24 (Table S2 in the Supplementary Appendix). The noninferiority of dolutegravir to EFV400 could be concluded if the lower limit of the two-sided 95% confidence interval for the difference between the two groups in the proportion of participants with a viral load of less than 50 copies per milliliter was above −10 percentage points. This margin was chosen for its consistency across other trials and European and FDA recommendations. A sample of 606 participants (303 per group)	Y / PY / PN / N / NI

	would provide the trial with 90% power to show noninferiority in the intention-to-treat analysis with the use of a one-sided significance level of 0.025, as recommended, and a noninferiority margin of 10 percentage points; a 10% increase in the sample size would maintain the same power in the per-protocol analysis (with the assumption that 10% of the participants might be excluded). Subsequent testing for superiority was to be performed if noninferiority was shown without the need to adapt the type I error rate. Analyses of efficacy, safety, and patient-reported outcomes were performed in the intention-to-treat population, since the efficacy and safety populations were identical in the trial. *Research paper, page 3*	
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	The primary endpoint is the proportion of patients with HIV viral load <50 copies/mL at week 48 using the FDA snapshot algorithm. *Supplementary* At week 48, a total of 231 of 310 participants (74.5%) in the dolutegravir group and 209 of 303 participants (69.0%) in the EFV400 group had a viral load of less than 50 copies per	Y / PY / PN / N / NI

	milliliter (Fig. 2). The difference between treatment groups was 5.5 percentage points (95% confidence interval [CI], −1.6 to 12.7), thus meeting the criterion for noninferiority (P<0.001) but not for superiority (P = 0.13) *Research paper, page 6*	
5.3 ... multiple eligible analyses of the data?	The primary analysis examined the difference between treatment groups in the proportion of participants with a viral load of less than 50 copies per milliliter at week 48, which was to be first tested for noninferiority in the intention-to-treat and per-protocol populations and then tested for superiority at a two-sided significance level of 0.05 if noninferiority was shown (Table S2 in the Supplementary Appendix). The noninferiority of dolutegravir to EFV400 could be concluded if the lower limit of the two-sided 95% confidence interval for the difference between the two groups in the proportion of participants with a viral load of less than 50 copies per milliliter was above −10 percentage points. This margin was chosen for its consistency across other trials and European and FDA recommendations. *Research paper, page 3* At week 48, a total of 231 of 310 participants (74.5%) in the dolutegravir group and 209 of	Y / PY / PN / N / NI

	303 participants (69.0%) in the EFV400 group had a viral load of less than 50 copies per milliliter (Fig. 2). The difference between treatment groups was 5.5 percentage points (95% confidence interval [CI], −1.6 to 12.7), thus meeting the criterion for noninferiority (P<0.001) but not for superiority (P = 0.13) *Research paper, page 6*	
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Low / High / Some concerns

APPENDIX 3. Costing table for treatment-naive PLHIV (without TB co-infection)

<table>
<tr><th>Parameter</th><th>Intervention
Tenofovir/lamivudine/dolutegravir (TLD)</th><th>Comparator
Tenofovir/lamivudine/efavirenz (TLEfv)</th><th>Reference</th></tr>
<tr><td>Unit cost of medicine
(A)</td><td><table><tr><th>Drug</th><th>Price (PHP)</th></tr><tr><td>TLD</td><td>549.00</td></tr></table>
Note: Price indicated is cost per bottle, already good for 1 month of supply</td><td><table><tr><th>Drug</th><th>Price (PHP)</th></tr><tr><td>TLEfv</td><td>549.00</td></tr></table>
Note: Price indicated is cost per bottle, already good for 1 month of supply</td><td>2021 DOH Annual Procurement Plan</td></tr>
<tr><td>Number of dosage units per treatment course
(B)</td><td><table><tr><th>Drug</th><th># ot tablets</th><th>frequency per day</th><th>Total tablets per day</th></tr><tr><td>TLD</td><td>1</td><td>1</td><td>1</td></tr></table></td><td><table><tr><th>Drug</th><th># ot tablets</th><th>frequency per day</th><th>Total tablets per day</th></tr><tr><td>TLEfv</td><td>1</td><td>1</td><td>1</td></tr></table></td><td>WHO. (2019). Update of Recommendations on First-and Second-Line Antiretroviral Regimens. In WHO Guidelines. Retrieved from http://apps.who.int/bookorders.</td></tr>
<tr><td>Duration of treatment
(C)</td><td>Lifetime treatment:
for annual comparative cost: 12 months
for budget impact analysis: 5 years</td><td>Lifetime treatment:
for annual comparative cost: 12 months
for budget impact analysis: 5 years</td><td>For the duration of treatment:
WHO. (2019). Update of Recommendations on First-and Second-Line Antiretroviral Regimens. In WHO Guidelines. Retrieved from http://apps.who.int/bookorders.

For number of years in BIA:
Health Technology Assessment Unit. (2020). Philippine HTA Methods Guide. Retrieved from Department of Health - Philippines</td></tr>
</table>

<table>
<tr>
<td>Total direct cost per patient per treatment course (D) = A*B*C</td>
<td>
<table>
<tr><th>Drug</th><th>Unit cost (PHP)</th><th># of months</th><th>Total cost</th></tr>
<tr><td>TLD</td><td>549.00</td><td>12</td><td>PHP 6,508.00</td></tr>
</table>
</td>
<td>
<table>
<tr><th>Drug</th><th>Unit cost (PHP)</th><th># of months</th><th>Total cost</th></tr>
<tr><td>TLD</td><td>549.00</td><td>12</td><td>PHP 6,508.00</td></tr>
</table>
</td>
<td>NA</td>
</tr>
<tr>
<td>Other medical cost associated with the use of the drug
(E)</td>
<td colspan="2"><u>Human resource</u>
Compensation for health professionals in treatment hubs
<table>
<tr><th rowspan="2">Professional</th><th colspan="2">Cost per patient (PHP)</th></tr>
<tr><th>Intervention</th><th>Comparator</th></tr>
<tr><td>Physician</td><td>1100</td><td>1100</td></tr>
<tr><td>Nurse</td><td>1540</td><td>1540</td></tr>
<tr><td>Pharmacist</td><td>220</td><td>220</td></tr>
<tr><td>Social worker</td><td>250</td><td>250</td></tr>
<tr><td>Case manager - enrollment</td><td>345</td><td>345</td></tr>
<tr><td>Case manager - Retention</td><td>1050</td><td>1050</td></tr>
<tr><td>Data manager</td><td>50</td><td>50</td></tr>
<tr><td>Administrative personnel</td><td>50</td><td>50</td></tr>
<tr><td>Total</td><td>4605.00</td><td>4605.00</td></tr>
</table>
Note: The other medical costs associated with the use of the drug for both the intervention and the comparator are at parity.</td>
<td>Costs for human resource:
Philippine Health Sector HIV Strategic Plan 2020-2022 Costing Worksheet.</td>
</tr>
<tr>
<td>Total treatment cost per patient (F) = D+E</td>
<td>
<table>
<tr><th></th><th>Cost (PHP)</th></tr>
<tr><td>Direct cost per patient per treatment course</td><td>6,508.00</td></tr>
</table>
</td>
<td>
<table>
<tr><th></th><th>Cost (PHP)</th></tr>
<tr><td>Direct cost per patient per treatment course</td><td>6,508.00</td></tr>
</table>
</td>
<td>NA</td>
</tr>
</table>

	Human resource: 4,605.00 **Total: 11,193.00**	Human resource: 4,605.00 **Total: 11,193.00**	
Expected number of patients who will use the drug **(G)**	**Total users for annual comparative costing** **Population** / **Proportion** / **Reference** Total PLHIV for year 1 — 19,888 — Estimated from the data provided by the DOH-EB Total PLHIV with TB coinfection for year 1 — 2,518 — Projected number provided by the DOH-DPCB **Total = 1-2** — **17,370** — NA **Note:** The expected number of patients who will use the drug for both the intervention and the comparator are at parity. **Total users for 5-year BIA** *Total PLHIV cases* **Year** / # of users per year = # of prevalent cases + # of incident cases Year 1: 19,888 | 19,888 Year 2: 43,555 | 19,888 | 23,667 Year 3: 71,718 | 19,888 | 23,667 | 28163 Year 4: 105,233 | 19,888 | 23,667 | 28,163 | 33514 Year 5: 145,115 | 19,888 | 23,667 | 28,163 | 33,514 | 39882 Legend: # of prevalent cases for that year - # of incident cases for that year - *Total PLHIV with TB co-infection*		Data submissions by the DOH-DPCB and DOH-EB, upon the request of the DOH-HTAU

Year	# of users per year = # of prevalent cases + # of incident cases					
Year 1	2,518	2,518				
Year 2	5,091	2,518	2,573			
Year 3	7,720	2,518	2,573	2,628		
Year 4	10,405	2,518	2,573	2,628	2,685	
Year 5	13,148	2,518	2,573	2,628	2,685	2,743

Legend:
# of prevalent cases for that year -
# of incident cases for that year -

Total PLHIV without TB co-infection

Year	# of PLHIV	# of PLHIV with TB	# of PLHIV without TB
Year 1	19,888	2,518	**17,370**
Year 2	43,555	5,091	**38,464**
Year 3	71,718	7,720	**63,999**
Year 4	105,233	10,405	**94,828**
Year 5	145,115	13,148	**131,967**

Assumptions:
- 19% annual growth rate for overall treatment-naive PLHIV (from EB data)
- 2.16% annual growth rate for treatment-naive PLHIV with TB co-infection (from DPCB data)
- Calculation did not include % of users failing treatment and switching out from the treatment
- Calculation did not include mortality rate

Total cost of delivering/ implementing the drug for the expected number of patients **(H)**	**PHP 194,423,334.01 - PHP 1,477,106,172.52**	**PHP 194,423,334.01 - PHP 1,477,106,172.52**	NA

= F*G			

APPENDIX 4. Costing table for treatment-experienced PLHIV

<table>
<tr><th>Parameter</th><th>Intervention
Tenofovir/lamivudine/dolutegravir (TLD)</th><th>Comparator
Lopinavir with ritonavir (LPV/r) + Zidovudine/Lamivudine (AZT/3TC)</th><th>Reference</th></tr>
<tr><td>Unit cost of medicine
(A)</td><td><table><tr><th>Drug</th><th>Price (PHP)</th></tr><tr><td>TLD</td><td>549.00</td></tr></table>Note: Price indicated is cost per bottle, already good for 1 month of supply</td><td><table><tr><th>Drug</th><th>Price (PHP)</th></tr><tr><td>LPV/r</td><td>1,630.48</td></tr><tr><td>AZT/3TC</td><td>453.75</td></tr></table>Note: Price indicated is cost per bottle, already good for 1 month of supply</td><td>2021 DOH Annual Procurement Plan</td></tr>
<tr><td>Number of dosage units per treatment course
(B)</td><td><table><tr><th>Drug</th><th># ot tablets</th><th>frequency per day</th><th>Total tablets per day</th></tr><tr><td>TLD</td><td>1</td><td>1</td><td>1</td></tr></table></td><td><table><tr><th>Drug</th><th># ot tablets</th><th>frequency per day</th><th>Total tablets per day</th></tr><tr><td>LPV/r</td><td>2</td><td>2</td><td>4</td></tr><tr><td>AZT/3TC</td><td>1</td><td>2</td><td>2</td></tr></table></td><td>WHO. (2019). Update of Recommendations on First-and Second-Line Antiretroviral Regimens. In WHO Guidelines. Retrieved from http://apps.who.int/bookorders.</td></tr>
<tr><td>Duration of treatment
(C)</td><td>Lifetime treatment:
for annual comparative cost: 12 months
for budget impact analysis: 5 years</td><td>Lifetime treatment:
for annual comparative cost: 12 months
for budget impact analysis: 5 years</td><td>For the duration of treatment: WHO. (2019). Update of Recommendations on First-and Second-Line Antiretroviral</td></tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td>Regimens. In WHO Guidelines. Retrieved from http://apps.who.int/bookorders.

For number of years in BIA: Health Technology Assessment Unit. (2020). Philippine HTA Methods Guide. Retrieved from Department of Health - Philippines</td>
</tr>
<tr>
<td>Total direct cost per patient per treatment course (D) = A*B*C</td>
<td>
<table>
<tr><th>Drug</th><th>Unit cost (PHP)</th><th># of months</th><th>Total cost</th></tr>
<tr><td>TLD</td><td>549.00</td><td>12</td><td>PHP 6,508.00</td></tr>
</table>
</td>
<td>
<table>
<tr><th>Drug</th><th>Unit cost (PHP)</th><th># of months</th><th>Total cost</th></tr>
<tr><td>LPV/r</td><td>1630.48</td><td>12</td><td>PHP 19,565.76</td></tr>
<tr><td>AZT/3TC</td><td>453.75</td><td>12</td><td>PHP 5,445.00</td></tr>
<tr><td colspan="3"></td><td>PHP 25,010.76</td></tr>
</table>
</td>
<td>NA</td>
</tr>
<tr>
<td>Other medical cost associated with the use of the drug
(E)</td>
<td colspan="2"><u>Human resource</u>
Compensation for health professionals in treatment hubs

<table>
<tr><th rowspan="2">Professional</th><th colspan="2">Cost per patient (PHP)</th></tr>
<tr><th>Intervention</th><th>Comparator</th></tr>
<tr><td>Physician</td><td>1100</td><td>1100</td></tr>
<tr><td>Nurse</td><td>1540</td><td>1540</td></tr>
<tr><td>Pharmacist</td><td>220</td><td>220</td></tr>
<tr><td>Social worker</td><td>250</td><td>250</td></tr>
<tr><td>Case manager - enrollment</td><td>345</td><td>345</td></tr>
<tr><td>Case manager - Retention</td><td>1050</td><td>1050</td></tr>
<tr><td>Data manager</td><td>50</td><td>50</td></tr>
</table>
</td>
<td>Costs for human resource:
Philippine Health Sector HIV Strategic Plan 2020-2022 Costing Worksheet.</td>
</tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td>Administrative personnel</td><td>50</td><td>50</td></tr>
<tr><td>Total</td><td>4,605.00</td><td>4,605.00</td></tr>
</table>
Note: The other medical costs associated with the use of the drug for both the intervention and the comparator are at parity.
</td><td></td></tr>
<tr><td>Total treatment cost per patient (F) = D+E</td><td>
<table>
<tr><th></th><th>Cost (PHP)</th></tr>
<tr><td>Direct cost per patient per treatment course</td><td>6,508.00</td></tr>
<tr><td>Human resource</td><td>4,605.00</td></tr>
<tr><td>Total</td><td>11,193.00</td></tr>
</table>
<table>
<tr><th></th><th>Cost (PHP)</th></tr>
<tr><td>Direct cost per patient per treatment course</td><td>25,010.76</td></tr>
<tr><td>Human resource</td><td>4,605.00</td></tr>
<tr><td>Total</td><td>29,615.76</td></tr>
</table>
</td><td>NA</td></tr>
<tr><td>Expected number of patients who will use the drug
(G)</td><td>
<u>Total users for annual comparative costing</u>
<table>
<tr><th>Population</th><th>Proportion</th><th>Reference</th></tr>
<tr><td>(1) PLHIV with severe adverse events to TLEfv</td><td>5,329</td><td>Estimated from the data provided by the DOH-DPCB</td></tr>
<tr><td>(2) PLHIV failing in AZT-based and ABC-based regimen</td><td>255</td><td>Estimated from the data provided by the DOH-DPCB</td></tr>
<tr><td>(3) PLHIV currently on NVP-based and RPV-based regimen</td><td>2,692</td><td>Estimated from the data provided by the DOH-DPCB</td></tr>
<tr><td>Total (1+2+3)</td><td>8,276</td><td>NA</td></tr>
</table>
Note: The expected number of patients who will use the drug for both the intervention and the comparator are at parity.

<u>Total users for 5-year BIA</u>

Total PLHIV cases
</td><td>Data submissions by the DOH-DPCB and DOH-EB, upon the request of the DOH-HTAU</td></tr>
</table>

	<table><tr><th>Subpopulation</th><th>Year 1</th><th>Year 2</th><th>Year 3</th><th>Year 4</th><th>Year 5</th></tr><tr><td>PLHIV with severe adverse events to TLEfv</td><td>5,329</td><td>5,521</td><td>5,675</td><td>5,833</td><td>5,995</td></tr><tr><td>PLHIV failing in AZT-based and ABC-based regimen</td><td>255</td><td>272</td><td>271</td><td>269</td><td>268</td></tr><tr><td>PLHIV currently on NVP-based and RPV-based regimen</td><td>2,692</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>Total</td><td>8,276</td><td>5,793</td><td>5,945</td><td>6,102</td><td>6,263</td></tr><tr><td>Cumulative total (incidence of present year + prevalence of previous year)</td><td>8,276</td><td>14,069</td><td>20,014</td><td>26,117</td><td>32,380</td></tr></table> Assumptions: ● 2.78% growth rate for PLHIV with severe ADR to TLEfv ● -0.49% growth rate for those failing AZT-based and ABC-based regimens ● PLHIV on NVP-based and RPV-based regimens will be completely transitioned after Y1 ● Calculation did not include % of users failing treatment and switching out from the treatment ● Calculation did not include mortality rate ● Cumulative number of cases since HIV treatment is lifetime	
Total cost of delivering/ implementing the drug for the expected number of patients **(H)** = F*G	**PHP 92,633,268.00 - PHP 362,426,854.98**	**PHP 245,100,029.76 - PHP 958,951,733.64**	NA