EU Risk Management Plan for
Truvada®
(Emtricitabine/Tenofovir Disoproxil Fumarate)

EU RISK MANAGEMENT PLAN FOR TRUVADA (EMTRICITABINE/TENOFOVIR DISOPROXIL FUMARATE)

RMP version to be assessed as part of this application:

Version number:	Data lock point for this RMP:	Date of final sign off:
20.0	08 May 2025	28 October 2025

Rationale for submitting an updated RMP:

This RMP was updated to remove:

- Missing information of:
  - Safety in pregnancy
  - Safety in lactation
- Additional pharmacovigilance activities of:
  - Antiretroviral pregnancy registry
- Targeted questionnaires corresponding to the previously removed important identified bone and renal risks.

Summary of significant changes in this RMP:

Part	Module/Annex	Significant changes to RMP
Part I Product Overview	N/A	None.
Part II Safety Specification	Section Part II: Module SI: Epidemiology of the indication and target populations(s)	None.
	Section Part II: Module SII: Nonclinical part of the safety specification	None.
	Section Part II: Module SIII: Clinical trial exposure	None.
	Section Part II: Module SIV: Populations not studied in clinical trials	Updated to reflect the removal of “safety in pregnancy” and “safety in lactation” as missing information.
	Section Part II: Module SV: Postauthorization experience	Postmarketing exposure updated.
	Section Part II: Module SVI: Additional EU requirements for the safety specification	None.

Part	Module/Annex	Significant changes to RMP
	Section Part II: Module SVII: Identified and potential risks	Updated to reflect the removal "safety in pregnancy" as missing information. Updated to reflect the removal of "safety in lactation" as missing information.
	Section Part II: Module SVIII: Summary of the safety concerns	Updated list of safety concerns.
Part III Pharmacovigilance Plan		Revised to reflect the removal of the targeted questionnaires on bone and renal events. The removal of the Antiretroviral Pregnancy Registry (APR) from additional pharmacovigilance activities.
Part IV Plan for postauthorization efficacy studies		None.
Part V Risk Minimization Measures		Revised to reflect the updated list of safety concerns (removal of "safety in pregnancy" from missing information) and the consequent removal of the antiretroviral pregnancy registry as an additional pharmacovigilance activity. Removal of "safety in lactation" as missing information.
Part VI Summary of RMP		Revised to reflect the updated list of safety concerns (removal of "safety in pregnancy" from missing information) and the consequent removal of the antiretroviral pregnancy registry as an additional pharmacovigilance activity. Removal of "safety in lactation" as missing information.
Part VII Annexes		Annexes 2, 3, 4 and 8 were updated to reflect the removal of the targeted questionnaires on bone and renal events, the removal of the antiretroviral pregnancy registry and/or the removal of "Safety in Pregnancy" from missing information, as applicable. Annex 8 was updated to reflect the removal of "safety in lactation" as missing information.

Other RMP versions under evaluation:

No other RMP versions are under evaluation.

Details of the currently approved RMP:

Version number:	Approved with procedure	Date of approval (opinion date)
19.0	EMEA/H/C/000594/WS2320/0177	12 January 2023

QPPV name: Rainer Heissing

QPPV signature: The RMP has been reviewed and approved by the QPPV and the electronic signature is on file.

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	adverse drug reaction
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
APR	Antiretroviral Pregnancy Registry
ART	antiretroviral therapy
ARV	antiretroviral
AS-PCR	allele-specific polymerase chain reaction
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BMD	bone mineral density
BUN	blood urea nitrogen
CCDS	company core data sheet
CD4	cluster of differentiation (antigenic marker on helper/inducer T cells)
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CKD	chronic kidney disease
CL_{cr}	creatinine clearance
dATP	deoxyadenosine triphosphate
ddI	didanosine
DEXA	dual energy X-ray absorptiometry
DF	disoproxil fumarate
DHHS	Department of Health and Human Services
DLP	data lock point
DNA	deoxyribonucleic acid
DRV	darunavir
DTG	dolutegravir
EACS	European AIDS Clinical Society
EAP	expanded access programme
EASL	European Association for the Study of the Liver
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EU-RMP	European Union Risk Management Plan
FTC	Emtriva® (emtricitabine)

GERS	Groupement pour l'Élaboration et al Réalisation de Statistiques
GFR	glomerular filtration rate
GI	gastrointestinal
GVP	Good Pharmacovigilance Practice
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HCP	Healthcare professional
HCV	hepatitis C virus
HIV (HIV-1)	human immunodeficiency virus (type 1)
IDU	injection drug user
iPrex	Pre-exposure Prophylaxis Initiative
IL	interleukin
INN	international nonproprietary name
INSTI	integrase strand transfer inhibitor
MAH	marketing authorization holder
MSM	men who have sex with men
N/A	not applicable
NIH	National Institute of Health
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
PEP	postexposure prophylaxis
PK	Pharmacokinetic
PI	protease inhibitor
PIL	patient information leaflet
PIP	Pediatric Investigational Plan
PRAC	Pharmacovigilance Risk Assessment Committee
PrEP	pre-exposure prophylaxis
PRT	proximal renal tubulopathy
PSUR	periodic safety update report
PYFU	person-years of follow up
QD	quaque die (once daily)
QPPV	qualified person for pharmacovigilance
RMP	Risk Management Plan
RNA	ribonucleic acid
RPV	rilpivirine
RT	reverse transcriptase
RTV	ritonavir
SD	standard deviation
SIV	simian immunodeficiency virus
SmPC	Summary of Product Characteristics

TAF	tenofovir alafenamide
TFV	tenofovir
TFV-DP	tenofovir-diphosphate
TDF	Viread® (tenofovir disoproxil fumarate)
TB	tuberculosis
TVD	Truvada® (FTC/TDF)
UDS	unscheduled DNA synthesis
UK	United Kingdom
ULN	upper limit of normal
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNODC	United Nations Office on Drugs and Crime
US	United States

PART I: PRODUCT OVERVIEW

Table Part I.1. Product Overview

Active substance(s) (INN or common name):	Emtricitabine (FTC)/tenofovir disoproxil fumarate (tenofovir DF [TDF])
Pharmaco-therapeutic group(s) (ATC Code):	Antivirals for the treatment of human immunodeficiency virus (HIV) infections, combinations (J05AR03)
Marketing Authorization Holder:	Gilead Sciences Ireland UC
Medicinal products to which this RMP refers:	1
Invented name(s) in the European Economic Area (EEA)	Truvada
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Emtricitabine: nucleoside reverse transcriptase inhibitor (NRTI) Tenofovir disoproxil fumarate: nucleotide reverse transcriptase inhibitor (NtRTI)
	Summary of mode of action: Emtricitabine (FTC) is a nucleoside analogue of 2'-deoxycytidine. Intracellularly, FTC is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate, the active metabolite, which competitively inhibits HIV reverse transcriptase, resulting in DNA chain termination. Tenofovir disoproxil fumarate (TDF), an oral prodrug of tenofovir, is a NtRTI. Following absorption, TDF is rapidly converted to tenofovir, which is metabolized intracellularly to the active metabolite, tenofovir diphosphate. Tenofovir diphosphate inhibits viral polymerases by direct binding competition with the natural deoxyribonucleotide substrate (deoxyadenosine triphosphate, dATP) and, after incorporation into DNA, by DNA chain termination.
	Important information about its composition: None
Hyperlink to the Product Information	Truvada Summary of Product Characteristics (SmPC)
Indication(s) in the EEA	Current: *Treatment of HIV-1 infection:* Truvada is indicated in antiretroviral combination therapy for the treatment of HIV-1 infected adults. Truvada is also indicated for the treatment of HIV-1 infected adolescents, with NRTI resistance or toxicities precluding the use of first line agents. *Pre-exposure prophylaxis (PrEP)*: Truvada is indicated in combination with safer sex practices for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in adults and adolescents at high risk.
	Proposed: None

Dosage in the EEA	Current: *Treatment of HIV-1 infection in adults and adolescents aged 12 years and older, weighing at least 35 kg*: One tablet, taken orally, once daily preferably with food. *Prevention of HIV in adults and adolescents aged 12 years and older weighing at least 35 kg*: One tablet, taken orally, once daily preferably with food.
	Proposed: None
Pharmaceutical form(s) and strengths	Current: Film-coated tablet containing 200 mg emtricitabine and 300 mg tenofovir DF
	Proposed: None
Is/Will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1. HIV Infection

SI.1.1. Incidence

The estimated number of people (adults and children) acquiring HIV infection in 2019 was 1.7 million (95% confidence interval [CI]: 1.2 million - 2.2 million), resulting in a 23% decline since 2010 (Table SI.1) {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}. Among adults (15 years and older), there was a 17% decline between 2010 and 2019, with the total number of new adult infections in 2019 estimated at 1.5 million (95% CI: 1.1-2.0 million) {UNAIDS AidsInfo 2020b}. Among children (<15 years old), the number of new infections in 2019 (n=150,000 [95% CI: 94,000 - 240,000]) declined by 52% during the same time (2010 to 2019){UNAIDS AidsInfo 2020c}.

However, incidence rates vary considerably and different trends over time exist by region and within country and region due to differences in structural and societal determinants across the globe. Notable declines in the number of new HIV infections overall have been observed in Eastern and Southern Africa (38%), the Caribbean (29%), Western and Central Africa (25%), Western and Central Europe and North America (15%), and Asia and the Pacific (12%). The introduction of oral pre-exposure prophylaxis (PrEP) for the prevention of HIV-1 infection in 2012 as an additional means of prevention has contributed to the decline of HIV transmission among gay men and other men who have sex with men (MSM), transgender persons, and sex workers, particularly in areas of North America, Europe, and Australia {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}. Globally, however, PrEP access and HIV prevention services in general are not uniform, and HIV incidence continues to increase in some regions. New HIV infections have been on the rise in Eastern Europe and Central Asia, with an increase of 72% between 2010 and 2019, largely due to transmission among injection drug users (IDU) and their sexual partners, as well as political and technical barriers to HIV prevention and treatment programs. The Middle East and North Africa and Latin America regions have also seen an increase in the number of new infections since 2010 (by 25% and 21%, respectively), where stigma against those living with HIV and lack of resources for HIV prevention and treatment programs are major barriers to preventing infection and ART access. Disparate groups within these and other regions also experience disproportionately higher rates of HIV incidence, such as adolescent girls and young women in Eastern and Southern Africa, children in Western and Central Africa, and men who have sex with men (MSM) in certain countries within the Asian and the Pacific region{Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}.

SI.1.2. Prevalence

The distribution of HIV-infected individuals varies enormously across geographical regions. Approximately 36.2 million adults and 1.8 million children were living with HIV globally at the end of 2019 (total: 38.0 million; 95% CI: 31.6-44.5 million (Table SI.1) {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}. An estimated 0.6% (95% CI: 0.5-0.8%) of adults (15 years and above) worldwide are living with HIV, although the burden of the epidemic continues to vary considerably between countries and regions {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2017b}.

The Eastern and Southern Africa region is most severely affected, with an estimated 20.7 million (95% CI: 18.4-23.0 million) people living with HIV infection in 2019 {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020} Although this region comprises 6.2% of the global population, it accounts for over 50% of people living with HIV worldwide. Western and Central Africa is the second most affected region with 4.9 million (95% CI: 3.9-6.2 million) people living with HIV. In both these African regions, which are referred to collectively as Sub-Saharan Africa, prevalence is high among key populations including MSM, sex workers, IDUs, and sexual partners of these groups. After Sub-Saharan Africa, the region's most heavily affected are Eastern Europe and Central Asia and Latin America and the Caribbean where 0.5-1.1% of adults were living with HIV in 2019 {UNAIDS AidsInfo 2020d}. The Eastern Europe and Central Asia region is the only region where HIV prevalence remains on the rise. The number of people living with HIV in this region has more than tripled since 2000 and reached an estimated 1.7 million in 2019 (95% CI: 1.4-1.9 million), resulting largely from a surge of infections among IDUs and their sexual partners {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}.
In contrast, estimated regional prevalence is lower in Western and Central Europe and North America (0.3% [95% CI: 0.2-0.3]) in adults{UNAIDS AidsInfo 2020d}. In this region, although more than 81% of people living with HIV are accessing ART, unprotected sex between men continues to dominate patterns of HIV transmission. In the Western and Central Europe, stigma and discrimination within the health-care system persist as significant barriers to accessing HIV treatment among MSM, in addition to sex workers and IDUs {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}.

Table SI.1. Regional Prevalent and Incident Cases of HIV Infection in 2019

	Prevalent Cases (n; 95% CI)		Incident Cases (n; 95% CI)	
	Overall	Adults[a]	Overall	Adults[a]
Asia and Pacific	300,000 (210,000-390,000)	280,000 (200,000-370,000)	5.8 million (4.3-7.2 million)	5.7 million (4.2-7.1 million)
Caribbean	13,000 (8,700-19,000)	12,000 (8,000-17,000)	330,000 (270,000-400,000)	320,000 (260,000-390,000)
Eastern and Southern Africa	730,000 (580,000-940,000)	660,000 (520,000-850,000)	20.7 million (18.4-23.0 million)	19.6 million (17.5-21.8 million)
Eastern Europe and Central Asia	170,000 (140,000-190,000)	160,000 (140,000-190,000)	1.7 million (1.4-1.9 million)	1.6 million (1.4-1.8 million)
Latin America	120,000 (73,000-180,000)	120,000 (71,000-170,000)	2.1 million (1.4-2.8 million)	2.1 million (1.4-2.8 million)

	Prevalent Cases (n; 95% CI)		Incident Cases (n; 95% CI)	
	Overall	**Adults[a]**	**Overall**	**Adults[a]**
Middle East and North Africa	20,000 (11,000-38,000)	18,000 (9,500-36,000)	240,000 (170,000-400,000)	230,000 (160,000-380,000)
Western and Central Africa	240,000 (150,000-390,000)	190,000 (120,000-310,000)	4.9 million (3.9-6.2 million)	4.5 million (3.6-5.7 million)
Western and Central Europe and North America	65,000 (49,000-87,000)	65,000 (48,000-87,000)	2.2 million (1.7-2.6 million)	2.2 million (1.7-2.6 million)
Total [b]	**1.7 million (1.2-2.2 million)**	**1.5 million (1.1-2.0 million)**	**38.0 million (31.6-44.5 million)**	**36.2 million (30.2-42.5 million)**

a Aged 15 years and older.
b Numbers in the columns may not add up to match the totals exactly due to the effect of rounding.
Source: {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2017b, Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020, UNAIDS AidsInfo 2020e}

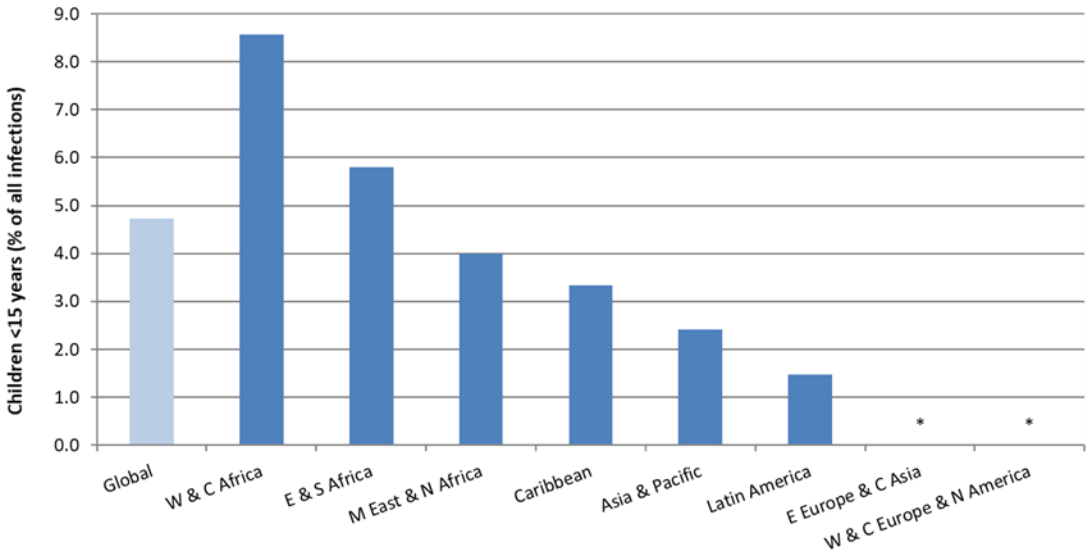
SI.1.3. Source: Demographics of the Population in the Authorized Indication

SI.1.3.1. HIV Infection in Children

Worldwide, 1.8 million (95% CI: 1.3-2.2 million) children (<15 years) were living with HIV in 2019, accounting for a substantial proportion of existing infections in Western and Central Africa (8.6%) and Eastern and Southern Africa (5.8%) {The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2018c}. Estimates of prevalence among children were unavailable for 2019 in in the Eastern Europe and Central Asia and Western and Central Europe and North America regions (Figure SI.1).

Mother-to-child transmission is the main route of infection among children, by which a woman infected with HIV passes HIV to her child through pregnancy, childbirth, or breast milk. If the mother has access to antiretroviral therapy (ART) during pregnancy, delivery, and breastfeeding, the risk of mother-to-child transmission reduces to 5% or less {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2016}. Expansions in ART and infant feeding-based prevention services are primarily responsible for the observed declines in the number of newly infected children {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2016}. It is estimated that since 1995, ART and prophylaxis to women living with HIV while pregnant or breastfeeding prevented 1.6 million children from acquiring HIV infection worldwide, with over 80% of those infections prevented between 2010 and 2015. Approximately 49% of all children who acquired HIV infection in 2019 were living in Eastern and Southern Africa, followed by Western and Central Africa (35%), Asia and Pacific (10%), Latin America (2%), and Caribbean (<1%) {UNAIDS AidsInfo 2020c} . The greatest reductions in HIV incidence among children between 2010 and 2019 were observed in Eastern and Southern Africa (63%), followed by Caribbean (55%), West and Central Africa (37%), Latin America (29%), and Asia and Pacific (21%) {UNAIDS AidsInfo 2020c} . However, the Middle East and North Africa region has yet to see a significant reduction in the number of children newly infected. This is likely attributable to the rates of mother-to-child transmission remaining high in the region (30% in 2019) due to low coverage of services for prevention of vertical transmission {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}.

Figure SI.1. Proportion of Individuals Infected with HIV Aged < 15 years by Geographical Region



* Data on individuals infected with HIV aged <15 years old not available for Eastern Europe & Central Asia and Western & Central Europe and North America.
Source: {UNAIDS AidsInfo 2020e, UNAIDS AidsInfo 2020f}

SI.1.3.2. HIV Infection by Gender

Worldwide, males comprised approximately 52% of total new infections (all ages) in 2019, while 48% were among females {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}. Since 2010, the annual number of new HIV infections has declined by 18% among males and 27% among females {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}. Differences in incidence rates exist globally, particularly in developing regions of the world, where societal gender inequalities, differential access to services, and sexual violence contribute to increased infection risk {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}. Women account for 63% of prevalent adult infections in Eastern and Southern Africa, 62% in Western and Central Africa, 47% in the Caribbean, 40% in Eastern Europe and Central Asia, 37% in Asia and Pacific, 36% in Middle East and North Africa, 30% in Latin America, and 23% in Western and Central Europe and North America {The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2018b}. Among young women (aged 15 to 24 years) incident infections reduced by 35% between 2010 and 2019, however, adolescent girls and young women still accounted for 19% of new adult HIV infections in 2019 and are globally twice as likely to become infected compared to men {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}. In sub-Saharan Africa, although women in this age group comprise only 10% of the total population, as high as 30% of new infections in this region are among young women {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}.

SI.1.3.3. HIV Infection by Age

There is evidence to suggest that the life expectancy of HIV patients is approaching that of HIV-negative persons, if diagnosis and treatment occur at an early enough stage and patients maintain adherence to treatment {Nakagawa 2013}. With increased life expectancy, the mean age of HIV patients continues to increase, and HIV is more prevalent among those who are older, particularly in countries where effective therapies were available earlier {Nakagawa 2013, Wing 2016}. Worldwide, between 1995 and 2013, prevalence rates among those aged 50 years and older have gradually increased over time; and the proportion of those living with HIV who are above the age of 50 ranged from 10% (in low- and middle-income countries) to 30% (in high income countries) {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2017a, Mahy 2014}. UNAIDS reports that this trend is largely due to the success of ART, decreases in HIV incidence among adults below the age of 50, and those above 50 having similar risk behaviors as those who are younger {UNAIDS 2013}.

SI.1.4. Main Existing Treatment Options

For ART-naïve HIV-1 infected patients, current treatment guidelines in the EU favour initial therapy with an unboosted integrase strand transfer inhibitor (INSTI) (dolutegravir [DTG] or bictegravir [BIC]) as the 3rd agent; recommended regimens consist of 2 nucleos(t)ide reverse transcriptase inhibitors (NRTIs) plus an INSTI (preferred regimen), 2 NRTIs plus either an non-nucleoside reverse transcriptase inhibitor (NNRTI) or a boosted protease inhibitor (PI) or 1 NRTI plus an INSTI. Treatment guidelines list emtricitabine/tenofovir alafenamide in combination with an INSTI (such as DTG, BIC, or raltegravir [RAL]), rilpivirine (RPV), ritonavir (RTV)- or cobicistat (COBI)-boosted darunavir (DRV) as one of the recommended regimens for initial therapy {European AIDS Clinical Society (EACS) 2020b}.

In the current US treatment guideline, the following are recommended regimens for ART-naive patients {Panel on Antiretroviral Guidelines for Adults and Adolescents 2019}:

- INSTI-Based Regimens:
  - BIC/tenofovir alafenamide (TAF)/emtricitabine (FTC)
  - DTG /abacavir/lamivudine—only for patients who are HLA-B*5701 negative
  - DTG plus tenofovir disoproxil fumarate (TDF)/FTC or TAF/FTC
  - RAL plus TDF/FTC or TAF/FTC
  - DTG plus lamivudine

While current combination antiretroviral (ARV) therapy for the treatment of HIV-1 infection is efficacious and well tolerated, these agents need to be taken every day and require near-perfect adherence to minimize the emergence of drug-resistant variants. As such, there remains a significant medical need for ARVs that can be administered less frequently (ie, long-acting drug products), thereby providing an alternative treatment option for PLWH.

Currently cabotegravir/rilpivirine is the only long-acting ARV regimen approved for the treatment of HIV-1 infection; cabotegravir/rilpivirine is currently only approved in Canada.

SI.1.5. Natural History of the Indicated Condition including Mortality and Morbidity

Untreated HIV compromises the host's immune system, which makes it susceptible to opportunistic infections and malignancies, and is associated with comorbidities that affect all organ systems. When untreated, HIV advances through three stages of infection: acute infection, clinical latency, and acquired immune deficiency syndrome (AIDS). The development of specific comorbidities and adverse events among those with HIV is dependent on a number of factors including stage of infection, the presence of coinfections, and treatment status. It is therefore difficult to provide frequency estimates of adverse events among the undiagnosed and untreated HIV population, which are also likely to differ substantially by geography, reflecting local conditions {Bradley 2014, Hamers 2008}. Although no effective cure currently exists, ART administered at an early enough stage can dramatically improve an HIV patient's prognosis, decreasing morbidity, mortality, and the risk of spreading the infection to others {Schwarcz 2013}. However, as the number of HIV patients with lifelong access to treatment is increasing, HIV-associated complications and chronic diseases related to inflammation, immunodeficiency, and ageing are also emerging {Deeks 2013a}.

SI.1.5.1. Mortality and Morbidity

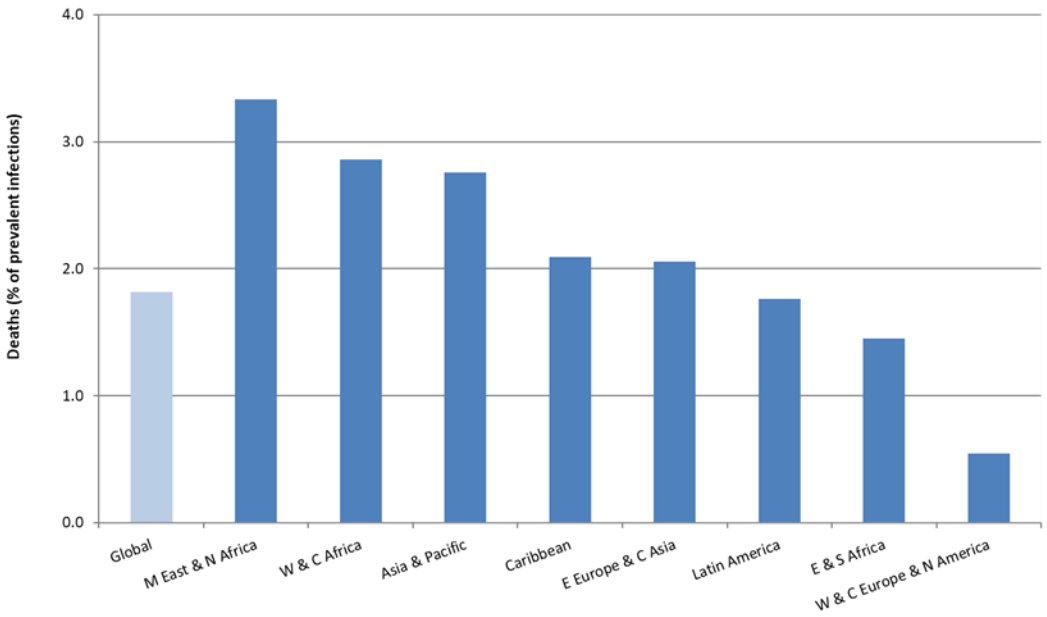
Access to effective treatment varies considerably, accounting for different rates of mortality by region. The number of people dying from AIDS-related causes began to decline in the mid-2000s because of scaled up ART and the steady decline in HIV incidence since the peak in 1997. Since its peak in 2004, AIDS-related deaths have reduced by more than 55% {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}. In 2019, this decline continued, with evidence that the drop in the number of people dying from AIDS-related causes is accelerating in several countries. In 2019, 690,000 (95% CI: 500,000-970,000) people died from AIDS-related causes worldwide, representing a 39% decline since 2010 {UNAIDS AidsInfo 2020a}. AIDS-related mortality among men tends to be higher than women worldwide, which is likely reflective of women being more likely to test for HIV, receive treatment, and adhere to treatment compared to men {UNAIDS 2018}. The leading cause of death among those living with HIV continues to be tuberculosis, which accounts for around one in three AIDS-related deaths {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}.

The number of people dying from AIDS-related causes in Eastern and Southern Africa declined by 49% from 2010 to 2019, although the region still accounted for 31% of all the people dying from AIDS in 2019 {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}. Declines in AIDS-related deaths between 2010 and 2019 also occurred in the Caribbean (37%), Western and Central Europe and North America (37%), Asia and Pacific (28%), Latin America (18%), Middle East and North Africa (2%). Eastern Europe and Central Asia, however, experienced a 24% increase in mortality from AIDS during the same time. Figure SI.2 provides regional variations in HIV related mortality (deaths as a percentage of prevalent HIV infections

in 2019) {The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2018a} {UNAIDS AidsInfo 2020a}.

Following the introduction of Highly Active Antiretroviral Therapy (HAART), mortality rates declined due to decreases in both non-AIDS and AIDS-related deaths, although the proportion of deaths associated with non-AIDS-related diseases has increased in patients on ART {Ingle 2014, Palella 2013, Weber 2013}. Common causes of non-AIDS-related deaths are non-AIDS-related malignancies, liver failure, non-AIDS-related infections, substance use-related, suicide, and myocardial infarction {Weber 2013}.

Figure SI.2. Regional Variation in HIV-Related Mortality



Source: {The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2018a}

SI.1.6. Important Co-morbidities and Co-infections

Prior to the success of ART for the treatment of HIV/AIDS, the most common co-morbidities were those traditionally defined as AIDS-related illnesses and correlated with CD4 cell count, such as Guillain-Barre Syndrome, Kaposi's sarcoma, and Non-Hodgkin's lymphoma {Hanson 1995}. As HIV patients on ART are living longer with viral suppression, the more prevalent co-morbidities are chronic health conditions in both resource-limited settings and wealthy regions {Deeks 2013b}, {Hirschhorn 2012}, {Balderson 2013}, {Hsue 2016}. Below is a list of important conditions that have evidence of higher risk among HIV patients and/or those accessing ART:

- Arthritis
- Bone disease (i.e, osteopenia, osteoporosis, and fracture)
- Cardiovascular disease (i.e, hypertension and hyperlipidemia)

- Chronic pain
- Endocrine disease, including diabetes
- Frailty
- Hepatitis
- Mental illness (i.e, depression and suicide ideation)
- Neurocognitive disorders
- Pulmonary disease (i.e, Chronic obstructive pulmonary disease)
- Renal disease
- Other sexually transmitted diseases
- Some non-HIV-related malignancies (i.e, liver, cervical, anal, and Hodgkin's lymphoma)
- Tuberculosis

SI.2. Pre-exposure Prophylaxis (PrEP)

HIV-1 pre-exposure prophylaxis (PrEP) involves the use of antiretroviral medication by HIV negative persons to reduce the risk of acquiring sexually transmitted HIV infection. Used in combination with other prevention strategies such as safer sex practices, it is a significant tool for addressing the global HIV epidemic. Truvada® (FTC/TDF) is the brand name for the fixed-dose, combination film-coated tablet that contains the active substances emtricitabine (FTC, Emtriva®) and tenofovir disoproxil fumarate (tenofovir DF, TDF, Viread®). Truvada was the first oral, once daily PrEP medication approved in July 2012 by the US Food and Drug Administration (FDA) for the prevention of HIV-1 infection among uninfected adults. Approval by the EU European Medicines Agency occurred in 2016, and the indication was expanded in May 2018 to include adolescents at high risk in December 2017. In the US, the indication was further expanded to include adults and adolescents, weighing at least 35 kilograms, at risk of HIV infection.

Currently, PrEP (either as F/TDF or generic F/TDx, or F/TAF) is approved for HIV prevention in over 80 countries worldwide. Globally, the reported number of people who received PrEP at least once in the previous year increased from 2000 in 2016 to greater than 590,000 in 2019.

PART II: MODULE SII - NONCLINICAL PART OF THE SAFETY SPECIFICATION

SII.1. Truvada

No nonclinical studies of Truvada have been conducted. Information on relevant safety findings for the components of Truvada are presented in the tables within this section. No additional studies are planned for Truvada.

SII.2. Emtricitabine

Table SII.1. Key Safety Findings from Nonclinical Studies (Emtricitabine)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Use
Nonclinical data on FTC reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development.	No safety concerns for humans are anticipated based on the non-clinical data for FTC

SII.3. Tenofovir DF

Table SII.2. Table of Key Safety Findings from Nonclinical Studies (Tenofovir DF)

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Use
Nonclinical safety pharmacology studies reveal no special hazard for humans (D990155, R990152, R990153, R990154). Findings in repeated dose toxicity studies in rats, dogs and monkeys at exposure levels greater than or equal to clinical exposure levels and with possible relevance to clinical use include renal and bone toxicity and a decrease in serum phosphate concentration. Evidence of renal toxicity was noted in four animal species exposed to TFV and TDF in nonclinical studies. Increases in serum creatinine, blood urea nitrogen (BUN), glycosuria, proteinuria, phosphaturia and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. In rats and mice, renal tubular karyomegaly was observed. In dogs and monkeys renal tubular degeneration/regeneration was observed in addition to karyomegaly. The incidence, severity and reversibility of the histopathological changes were related to dose and duration of treatment. These toxicities were noted at exposures (based on AUCs) 2–20 times higher than those observed in humans after a 300 mg daily dose.	*Renal toxicity is an important identified risk for TDF.* Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal renal tubulopathy (PRT) (including Fanconi syndrome) have been reported with the use of TDF (Truvada SmPC). *Bone events due to PRT / loss of BMD is an important identified risk for TDF.* Decreases in BMD observed following the initiation of ART appear to be greater with regimens containing TDF compared to those without TDF. In clinical studies of HIV-1 infected patients 2 to < 18 years of age and HBV infected patients 12 to < 18 years of age, small decreases in median BMD Z-scores were observed following treatment with TDF. The long-term clinical relevance of these observations is unknown. Osteomalacia (infrequently contributing to fractures) may be associated with PRT (Truvada SmPC).

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Use
Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (BMD) (rats and dogs). The bone toxicity in young adult rats and dogs occurred at exposures ≥ 5-fold the exposure in pediatric or adult patients; bone toxicity occurred in juvenile infected monkeys at very high exposures following subcutaneous dosing (≥ 40-fold the exposure in patients). Findings in the rat and monkey studies indicated that there was a substance-related decrease in intestinal absorption of phosphate with potential secondary reduction in BMD.	
Genotoxicity studies revealed positive results in the *in vitro* mouse lymphoma assay, equivocal results in one of the strains used in the Ames test, and weakly positive results in an unscheduled DNA synthesis (UDS) test in primary rat hepatocytes. However, it was negative in an *in vivo* mouse bone marrow micronucleus assay. Oral carcinogenicity studies in rats and mice only revealed a low incidence of duodenal tumors at an extremely high dose in mice.	These tumors are unlikely to be of relevance to humans.
Reproductive studies in rats and rabbits showed no effects on mating, fertility, pregnancy or fetal parameters. Tenofovir DF reduced the viability index and weight of pups in peri-postnatal toxicity studies at maternally toxic doses.	No safety concerns for humans are anticipated based on the non-clinical reproductive studies for TDF.

SII.4. Conclusions on Nonclinical Data

Table SII.3. Safety Concerns from Nonclinical Data

	Safety Concern
Important Identified Risks	Renal toxicity (TDF)
	Bone events due to PRT/loss of BMD (TDF)
Important Potential Risks	None
Missing Information	None

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

SIII.1. Clinical Trial Exposure

SIII.1.1. HIV-1 infection

The following tables provide clinical trial exposure to Truvada cumulative to 02 April 2018 in subjects with HIV-1 infection in the following populations:

All clinical trial populations including open extension phase based on data from:

- Completed studies: GS-01-934, GS-99-903 E, GS-DE-164-0106, GS-ES-164-0151, GS-ES-164-0154, GS-EU-164-0206, GS-FR-164-0109, GS-MC-164-0111, GS-US-164-0107, GS-US-164-0115, GS-US-164-0216, GS-US-216-0105, GS-US-216-0114, GS-US-236-0103, GS-US-236-0115, GS-US-236-0121, GS-US-236-0140, GS-US-299-0102

- Ongoing Open-label studies: GS-US-236-0128, GS-US-292-0109, GS-US-380-1961

- Ongoing Unblinded studies: GS-US-311-1089

Table SIII.1. Duration of Exposure to Truvada in Subjects with HIV-1 Infection

Duration of Exposure	Patients	Person-years
≥ 1 day	3305	6148
> 30 days	3206	6144
> 90 days	3094	6122
> 180 days	2660	5930
> 1 year	1973	5330
> 2 years	1343	4409
> 3 years	800	3079
> 4 years	280	1340
>5 years	59	340
>6 years	17	120
>7 years	12	89

Note: The exposure in person-years in Table SIII.1for duration of exposure ≥1 day do not match the total figures in Table SIII.2 and Table SIII.3 due to the effects of rounding of the values per age group, gender and racial origin.

Table SIII.2. Truvada Exposure by Age Group and Gender in Subjects with HIV-1 Infection

Age Groups	Patients		Person-years	
	Male	Female	Male	Female
18-30 yrs	433	143	985	223
31–40 yrs	790	262	1537	455
41–50 yrs	847	227	1574	378
51-65 yrs	448	118	765	185
66-75 yrs	32	3	44	2
>75 yrs	2	0	1	0
Total	**2552**	**753**	**4906**	**1243**

Table SIII.3. Truvada Exposure by Racial Origin in Subjects with HIV-1 Infection

Racial Origin	Patients	Person-years
White	2140	4010
Black or African American	718	1216
Asian	142	392
American Indian or Alaska Native	13	26
Native Hawaiian or other Pacific Islander	8	20
Multiple	84	233
Other	119	172
Not permitted	9	21
Missing	72	57
Total	**3305**	**6147**

SIII.1.2. PrEP

SIII.1.2.1. Non-Gilead Sponsored PrEP Studies

The safety and efficacy of once-daily oral Truvada in the prevention of HIV-1 acquisition among MSM have been demonstrated in a large (n = 2499), multinational, randomized, placebo-controlled, double-blind, Phase 3 study (iPrEx study [CO-US-104-0288]) {Grant 2010}. The safety and efficacy of once-daily oral Viread or Truvada in the prevention of HIV-1 acquisition among East African heterosexual men and women in 4747 HIV-1 serodiscordant partnerships were demonstrated in a randomized, placebo-controlled, double-blind, Phase 3 study (also known as the Partners PrEP study [CO-US-104-0380]) {Baeten 2012}. Exposure data from these trials is presented below:

Table SIII.4. Truvada vs. Placebo Exposure in the iPrEX trial (CO-US-104-0288)

Exposure (Weeks)[a]	Placebo (N = 1248)	FTC/TDF (N = 1251)	Total (N = 2499)
Mean	67.7	67.1	67.4
Standard Deviation	37.37	38.42	37.89
Minimum	0.1	0.1	0.1
Q1	37.8	36.3	36.9
Median	62.2	62.3	62.3
Q3	100.2	100.3	100.3
Maximum	144.1	145.1	145.1

a Exposure is calculated as the number of weeks from the date of first bottle dispensed to the first occurrence between date of recorded study drug termination or positive HIV-1 test. If neither of these events occurred, the exposure is calculated as the number of weeks from the date of first bottle dispensed to the first occurrence between final study treatment suspension, last bottle dispensing, or study termination.

Table SIII.5. Truvada vs. placebo Demographics in the iPrEX trial (CO-US-104-0288)

Characteristic		Placebo (n = 1248)	FTC/TDF (n = 1251)
Demographic			
Age – no. (%)	p = 0.04		
18–24		662 (53)	591 (47)
25–29		241 (19)	274 (22)
30–39		224 (18)	249 (20)
≥ 40		121 (10)	137 (11)
Race/Ethnicity – no. (%)	p = 0.40		
Black/African American		97 (8)	117 (9)
White		208 (17)	223 (18)
Mixed/Other		878 (70)	849 (68)
Asian		65 (5)	62 (5)
Hispanic/Latino – no. (%); p = 0.72		906 (73)	900 (72)

Table SIII.6. Truvada vs. placebo Exposure in the Partners PrEP trial (CO-US-104-0380)

	TDF (n=1584)	FTC/TDF (n=1579)	Placebo (n=1584)
Randomized, n (%)	1584 (100)	1579 (100)	1584 (100)
Person-years follow-up	2631	2638	2655

Table SIII.7. Truvada vs. placebo Demographics in the Partners PrEP trial (CO-US-104-0380)

	TDF N = 1584	FTC/TDF N = 1579	Placebo N = 1584
Demographic Characteristics, n (%) or Median (IQR)			
Gender			
Male	598 (38)	566 (36)	621 (39)
Female	986 (62)	1013 (64)	963 (61)
Age, years	32 (26, 39)	32 (26, 39)	33 (26, 39)
Age category			
18–24 years	268 (17)	287 (18)	273 (17)
25–34 years	657 (41)	636 (40)	629 (40)
35-44 years	474 (30)	460 (29)	509 (32)
≥ 45 years	185 (12)	196 (12)	173 (11)

Abbreviations: IQR = interquartile range

The demographic disposition and exposure to Truvada for PrEP from two Adolescent Trials Network (ATN) studies investigating TVD PrEP in HIV uninfected adolescents (Study ATN 113) and HIV uninfected young men (Study ATN 110) is also presented below.

Table SIII.8. Duration of Exposure to Truvada in uninfected Adolescent Subjects in Study ATN 113

Duration of Exposure	Patients
≥4 weeks (28 days)	65
≥8 weeks (56 days)	62
≥12 weeks (84 days)	61
≥24 weeks (168 days)	53
≥ 36 weeks (252 days)	42
≥ 48 weeks (336 days)	18

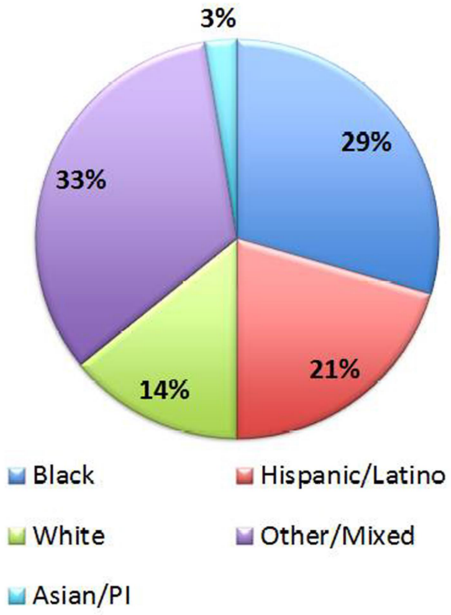
In Study ATN 113, 78 HIV-uninfected male subjects were enrolled{Hosek 2017a}. The demographic and baseline characteristics of subjects in Study ATN 113 are presented in Figure SIII.1 and the proportion by race of subjects is presented in Figure SIII.2. Male subjects aged between 15 and 17 years were enrolled, the mean age of subjects was 16.5 years {Hosek 2016}.

Figure SIII.1. ATN 113: Baseline Demographic data

Mean age	16.5
Sexual Identity	Gay – 58% Bisexual – 28% Questioning – 6%
Completed high school	18.4%
Currently living with parents/family	88.5%
Received public aid	76.9%
Kicked out of house for being gay	15%
Ever been paid for sex	17%
Partners in past mo	2
CRAI w/last partner	60%
Any positive STI test	15.4%

Abbreviations: CRAI = condomless receptive anal intercourse
Source: {Hosek 2016}

Figure SIII.2. ATN 113: Baseline Demographics (Race)



Source: {Hosek 2016}

In Study ATN 110, 200 HIV-uninfected male subjects were enrolled. The demographic and baseline characteristics of subjects in Study ATN 110 are presented in Table SIII.9. Male subjects aged between 18 and 22 years were enrolled with a median age of 20 years {Hosek 2017b}.

Table SIII.9. ATN 110: Baseline Demographic Data

	Overall (N=200)
Age at Baseline (years)	
Mean (SD)	20.2 (1.3)
Median	20.0
Race (%)	
Black/African American	96 (46.5)
Asian/Pacific Islander	2 (1.0)
White/non-Hispanic	42 (21.0)
White/Hispanic	21 (10.5)
Other/Mixed Race	42 (21.0)
Ethnicity (%)	
Hispanic or Latino	53 (26.5)
Non-Hispanic or Latino	145 (72.5)

Source: Baseline demographic data {Hosek 2017b}

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1. Exclusion Criteria in Pivotal Clinical Studies within the Development Program

Table SIV.1. Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Considered to be Missing Information
Exclusion Criteria from HIV-1 Studies		
Pregnant females and females who are breastfeeding	Limited information on the use in this patient population.	No Rationale: Based on the Antiretroviral Pregnancy Registry report (data to 31July 2024), sufficient numbers of first trimester exposures (Emtricitabine [n=5250], TDF [n=5076]) have been monitored with no increase in birth defects detected. The Truvada SmPC contains guidance on use during pregnancy and lactation.
Age < 18 years	The efficacy and safety of the emtricitabine and tenofovir DF components of Truvada was first established in the adult population.	No Rationale: Truvada is indicated for use in adolescents aged 12 years and older, weighing at least 35 kg based on clinical trial data for FTC and TDF in this patient population.
Inadequate renal function: Calculated creatinine clearance < 50 mL/min according to the Cockcroft-Gault formula	Tenofovir is primarily renally excreted by a combination of glomerular filtration and tubular secretion. Tenofovir PK is substantially altered in subjects with moderate and severe renal impairment.	No Rationale: Collection of further safety data for patients with renal impairment is no longer needed. The Truvada SmPC contains dosing recommendations in adults with renal impairment and guidance on how to monitor renal function in individuals at risk of for renal disease.
Patients receiving ongoing therapy with: • Nephrotoxic agents: aminoglycoside antibiotics, IV amphotericin B, cidofovir, cisplatin, foscarnet, IV pentamidine, other agents with significant nephrotoxic potential	Renal toxicity is an important identified risk for TDF.	No Rationale: Collection of further safety data for patients receiving these particular classes of drugs is not considered warranted, as the risk of co-administration can be predicted (e.g., risk of additive nephrotoxicity). The Truvada SmPC contains text recommending avoiding use of nephrotoxic agents with Truvada, and guidance that co-administration

Criterion	Reason for Exclusion	Considered to be Missing Information
• Agents that compete for elimination via active tubular secretion (probenecid, systemic chemotherapeutic agents, systemic corticosteroids, Interleukin 2 [IL 2])		of Truvada with medicinal products that reduce renal function or compete for active tubular secretion (e.g. cidofovir) may increase serum concentrations of emtricitabine, tenofovir and/or the co-administered medicinal products.
Exclusion Criteria From Truvada Studies for PrEP		
Subjects receiving therapy with: • Parenteral antibiotics • antiretrovirals (ARV; including nucleoside analogs, nonnucleoside reverse transcriptase inhibitors, protease inhibitors or investigational antiretroviral agents) • interferon (alpha, beta, or gamma) or interleukin (e.g., IL-2) therapy, • aminoglycoside antibiotics, • amphotericin B, • cidofovir, • systemic chemotherapeutic agents, other agents with significant nephrotoxic potential, • other agents that may inhibit or compete for elimination via active renal tubular secretion (e.g., probenecid), and/or other investigational agents	These medications could confound safety evaluation	No Rationale: Collection of further safety data for patients receiving these particular classes of drugs is not considered warranted, as the risk of co-administration can be predicted (e.g., risk of additive nephrotoxicity). The Truvada SmPC contains text recommending avoiding use of nephrotoxic agents with Truvada, and guidance that co-administration of Truvada with medicinal products that reduce renal function or compete for active tubular secretion (e.g. cidofovir) may increase serum concentrations of emtricitabine, tenofovir and/or the co-administered medicinal products. The Truvada SmPC also contains recommendations concerning co-administration of other antiretrovirals with Truvada.
Pregnant females and females who are breastfeeding	Limited information on the use in this patient population.	No Rationale: Based on the Antiretroviral Pregnancy Registry report (data to 31 July 2024), sufficient numbers of first trimester exposures (Emtricitabine [n=5250], TDF [n=5076]) have been monitored with no increase in birth defects detected. The Truvada SmPC contains guidance on use during pregnancy and lactation.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

Table SIV.2. Ability of the Clinical Trial Development Program to Detect Adverse Drug Reactions (HIV-1 treatment)

Ability to Detect Adverse Reactions	Limitation of Trial Program	Discussion of Implications for Target Population
Which are rare	3305 HIV-1 infected subjects were exposed to Truvada in clinical trials.	ADRs with a frequency of greater than 1 in 1102 (0.04%) could be detected if there were no background incidence.
Due to prolonged exposure	1343 HIV-1 infected subjects have been exposed to Truvada for at least 2 years and 800 HIV-1 infected subjects have been exposed to Truvada for at least 3 years in clinical trials.	No ADRs specifically associated with prolonged exposure to Truvada have been identified in clinical trials.
Due to cumulative effects	1343 HIV-1 infected subjects have been exposed to Truvada for at least 2 years and 800 HIV-1 infected subjects have been exposed to Truvada for at least 3 years in clinical trials.	No cumulative effects to Truvada have been identified in clinical trials.
Which have a long latency	1343 HIV-1 infected subjects have been exposed to Truvada for at least 2 years and 800 HIV-1 infected subjects have been exposed to Truvada for at least 3 years in clinical trials.	No ADRs to Truvada with a long latency have been identified in clinical trials.

Table SIV.3. Ability of the Clinical Trial Development Program to Detect Adverse Drug Reactions (PrEP)

Ability to Detect Adverse Reactions	Limitation of Trial Program	Discussion of Implications for Target Population
Which are uncommon	2827 subjects were exposed to Truvada during the iPrEx (CO-US-104-0288) and Partners PrEP (CO-104-0380).	ADRs with a frequency of greater than 1 in 942 (0.11%) could be detected if there were no background incidence.
Due to prolonged exposure	Mean and maximum exposure to Truvada was 67.1 and 145.1 weeks, respectively, in the iPrEX trial (CO-US-104-0288). Duration of exposure is not available for the Partners PrEP study (CO-104-0380).	No ADRs specifically associated with prolonged exposure to Truvada have been identified in the Truvada PrEP studies.
Due to cumulative effects	Mean and maximum exposure to Truvada was 67.1 and 145.1 weeks, respectively, in the iPrEX trial (CO-US-104-0288). Duration of exposure is not available for the Partners PrEP study (CO-104-0380).	No cumulative effects to Truvada have been identified in the Truvada PrEP studies.
Which have a long latency	Mean and maximum exposure to Truvada was 67.1 and 145.1 weeks, respectively, in the iPrEX trial (CO-US-104-0288). Duration of exposure is not available for the Partners PrEP study (CO-104-0380).	No ADRs to Truvada with a long latency have been identified in the Truvada PrEP studies.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table SIV4. Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of special population	Exposure	Considered to be Missing Information
Children (including long-term safety)	Subjects < 18 years were excluded from enrolling in Gilead-sponsored interventional clinical studies.	No Rationale: Truvada is indicated for use in adolescents aged 12 years and older, weighing at least 35 kg based on clinical trial data for FTC and TDF in this patient population.
Elderly	As of 02 April 2018, 37 subjects (47 patient-years) over 65 years old were exposed to Truvada in Gilead-sponsored interventional clinical studies.	No Rationale: Safety in elderly patients is monitored on an ongoing basis through routine pharmacovigilance activities and data are presented periodically in the Truvada periodic safety update report (PSUR). No safety concerns regarding use of Truvada in elderly patients have been identified.
Pregnant and breastfeeding women	Pregnant and breastfeeding women were excluded from enrolling in clinical studies. As of 02 April 2018, 79 pregnant subjects were exposed to Truvada in Gilead-sponsored interventional clinical trials. There were no cases of breastfeeding during treatment with Truvada in Gilead-sponsored interventional clinical studies.	No. Rationale: Based on the Antiretroviral Pregnancy Registry report (data to 31 July 2024), sufficient numbers of first trimester exposures (Emtricitabine [n=5250], TDF [n=5076]) have been monitored with no increase in birth defects detected. The Truvada SmPC contains guidance on use during pregnancy and lactation.
Patients with renal impairment	In the TDF HIV and HBV clinical trial programs, 304 subjects (301,085 person-days) with mild renal impairment and 18 subjects (11,592 person-days) with moderate/severe renal impairment have been exposed to TDF.	No Rationale: Safety in patients with renal impairment is monitored on an ongoing basis through routine pharmacovigilance activities and data are presented periodically in the Truvada periodic safety update report (PSUR). No safety concerns regarding use of Truvada in patients with renal impairment have been identified.
Patients with hepatic impairment	Patients with hepatic transaminases (AST and ALT) > 3 times the upper limit of the normal range (ULN) and total bilirubin >1.5mg/dL were excluded from the Truvada HIV development program.	No Rationale: The pharmacokinetics of tenofovir has been studied in patients with hepatic impairment and no dose adjustment is required for TDF in these patients. Based on minimal hepatic metabolism and the renal route of elimination for emtricitabine, it is unlikely that a dose adjustment would be required for Truvada in patients with hepatic impairment.

PART II: MODULE SV - POSTAUTHORIZATION EXPERIENCE

SV.1. PostAuthorization Exposure

SV.1.1. Method Used to Calculate Exposure

Patient exposure to marketed Truvada has been estimated from both sales data and from prescription data and is reported in PSURs. The methodology used to calculate patient exposure from these 2 sources is described below:

Sales Data

The number of bottles sold during the reporting period was multiplied by 30 to provide the number of tablets sold. As Truvada is taken as a once daily dose, the total number of tablets was divided by 365.25 to provide patient-years of treatment. It should be noted that the use of sales data for patient exposure calculations will generally overestimate patient exposure due to the accumulation of drug stocks at pharmacies/distributors.

Prescription Data

Estimates of the demographics data of HIV infected patients exposed to Truvada in the 5 major European countries United Kingdom (UK), France, Germany, Italy and Spain were obtained from the following sources:

- ***IQVIA/Groupement pour l'Élaboration et la Réalisation de Statistiques (GERS)*:** IQVIA data in the EU provides details of the number of bottles prescribed (no details are provided on whether a prescription is a repeat or an initial prescription). The data is obtained through a comprehensive panel of pharmacies and wholesalers. GERS data is based on a syndicate of manufacturers and wholesalers who provide their transactions and is available in France only; GERS data is combined with IQVIA data.

- ***Ipsos Monitor:*** The Ipsos Healthcare HIV EU Therapy Monitor study is a syndicated, bi-annual diary study involving HIV treating physicians and data has been obtained from April - June 2021. A total of 208 HIV treating physicians are involved across the main 5 European countries and the sample is regionally representative of the prevalence of HIV infection in each country. The physicians are screened to ensure they see at least 15 HIV patients per week and manage the care of at least 50 HIV patients. Each physician completes patient record forms for the next 8 patients they see during the fieldwork period. All patients are currently receiving ARV therapy and these patients could be patients initiating, switching or maintaining treatment. In the 5 major European countries (Q2'21), this dataset consists of 1631 patient records.

SV.1.2. Exposure

SV.1.2.1. Exposure Based on Sales Data

Cumulative global patient exposure to Truvada since first marketing approval in The United States on 02 August 2004 to 31 March 2025 is estimated to be 5,880,581 patient-years of treatment.

Postmarketing exposure is not presented by HIV and PrEP indication as it is not possible to separate postmarketing exposure by indication since postmarketing exposure is based on sales data and the same tablets are used for both the HIV and the PrEP indication.

Further information on cumulative patient exposure by geographic areas is provided in the PSUR for Truvada.

SV.1.2.2. Exposure Based on Prescription Data

Estimates of the demographics of HIV infected patients exposed to Truvada in the 5 major European countries, based on prescription data, indicate that most (72%) patients were male, and the majority (63%) of patients were aged between 20 – 39 years.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1. Potential for Misuse for Illegal Purposes

There are no data to suggest that there is potential for Truvada to be misused for illegal purposes.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1. Identification of Safety Concerns in the Initial RMP submission

Not applicable.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

No new important identified risks, important potential risks or missing information have been identified for Truvada since submission of the last RMP.

Missing information removed from the list of safety concerns, along with reasons for their removal, are presented in Table SVII.1

Table SVII.1. Reason for Removing an Important Identified or Potential Risk or Missing Information from the List of Safety Concerns in the RMP

Safety Concern Removed	Reason for Removal From the List of Safety Concerns
Missing information	
Safety in pregnancy and lactation.	Based on the Antiretroviral Pregnancy Registry report (data to 31 July 2024), for individual components of Truvada, sufficient numbers of first trimester exposures (Emtricitabine [n=5250], TDF [n=5076]) have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects in the more common classes, cardiovascular and genitourinary systems. No such increases have been detected to date. According to the Truvada EU SmPC, a large amount of data on pregnant women (more than 1,000 pregnancy outcomes) indicates no malformations or foetal/neonatal toxicity associated with emtricitabine and TDF. Additionally, management of this risk is fully integrated into standard clinical practice through inclusion in treatment guidelines {European Aids Clinical Society (EACS) 2025}. No further information on pregnancy is needed to further characterize this missing information. According to the Truvada EU SmPC, emtricitabine and tenofovir have been shown to be excreted in human milk. There is insufficient information on the effects of emtricitabine and tenofovir in newborns/infants. In order to avoid transmission of HIV to the infant, Truvada should not be used during breastfeeding. Additionally, management of this risk is fully integrated into standard clinical practice through inclusion in treatment guidelines {European Aids Clinical Society (EACS) 2025}. No further information on lactation is needed to further characterize this missing information and has been recommended for removal by PRAC under procedure EMA/VR/0000280828.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1. Important Identified Risks

The following important identified risks are described in the tables within this section

- HIV-1 acquisition, including infection resulting from non-adherence (PrEP indication) (Table SVII.2)
- Development of resistance in patients with unrecognized or acute HIV-1 infection (PrEP indication) (Table SVII.3)

Table SVII.2. HIV-1 Acquisition, Including Infection Resulting from Non-adherence (PrEP Indication) (TVD)

Important Identified Risk:	HIV-1 Acquisition, including infection resulting from non-adherence (PrEP indication)
Potential mechanisms	The lack of adherence to the daily dosing regimen is associated with reduced plasma concentrations of FTC and tenofovir (TFV), which could allow HIV-1 acquisition.
Evidence source and strength of evidence	HIV-1 acquisition has been reported infrequently with the use of Truvada for the PrEP indication in clinical trials, in the postmarketing setting and in the literature, and has been associated with poor adherence to the daily dosing scheme.
Characterisation of the risk	The use of TVD for a PrEP indication may not always prevent HIV-1 acquisition. In the iPrEx Study, the incidence of emergent HIV-1 seroconversion was 2.9% (36/1251) in the TVD group compared to 5.1% (64/1248) in the placebo group, representing a relative reduction of 42% in incidence. The prophylactic effectiveness of TVD is strongly correlated with adherence to the daily dosing regimen in the iPrEx study. In the Partners PrEP study, 82 post-randomization HIV-1 seroconversions were identified. Of those, 17 were in the TDF group (17 of 1584; 1.1%), 13 were in the FTC/TDF group (13 of 1579 subjects; 0.8%), and 52 were in the placebo group (52 of 1584 subjects; 3.3%), indicating a 75% relative reduction in HIV-1 infection risk with FTC/TDF compared with placebo (95% CI 55% 87%, $p < 0.0001$). The HIV-1 protective effects of FTC/TDF were not statistically different by level of study drug coverage ($\geq 90\%$ versus $< 90\%$); although only 12% of study follow-up time had $< 90\%$ study drug coverage by monthly pill counts. In Study ATN 113 (N=78; age range 15-18 years), 3 seroconversions occurred through 48 weeks of treatment with Truvada for PrEP in adolescent males (HIV incidence = 6.4 per 100 person-years; 95% CI: 0.0 to 13.7). Subjects who seroconverted had tenofovir-diphosphate (TFV-DP) levels consistent with < 2 doses per week on average, which was below the levels that were considered protective for PrEP (≥ 700 fmol/punch equivalent to ≥ 4 doses/week). In Study ATN 113, adherence decreased over the 48 week treatment period, as demonstrated by the levels of TFV-DP. This drop in TFV-DP levels coincided with the

Important Identified Risk:	HIV-1 Acquisition, including infection resulting from non-adherence (PrEP indication)
	change in the frequency of study visits from monthly to quarterly visits {Hosek 2017a, Hosek 2016}. In Study ATN 110 (N=200; age range 18-22 years), 4 seroconversions occurred during the study (1 event each at Week 4, 32, 40, and 48) for an HIV incidence rate of 3.29 per 100 person-years (95% CI 0.07 to 6.52). None of the subjects who seroconverted had detectable levels of TFV-DP in the sample that was drawn closest to the seroconversion date. As seen in study ATN 113, adherence also decreased over the 48-week treatment period. Subjects who reported condomless sex had higher levels of TFV-DP {Hosek 2017b}. The efficacy observed in clinical studies such as iPrEx and Partner's PrEP has been borne out in demonstration studies with only 67 seroconversions reported to date among the 8,478 recipients (7,002 men; 1,378 women; and 76 transgender women) of Truvada for PrEP, a rate of 0.95/100 person-year seroconversion rate (95% CI: 0.74, 1.21). These results are based on data collected from 32 individual studies from 16 countries evaluating the use of FTC/TDF for PrEP. Of those who seroconverted, 64 were men, 2 women, and 1 transgender woman, representing a seroconversion rate per 100 person-year (95% CI) of 1.03 (0.80-1.32), 0.25 (0.03-0.92), and 2.07 (0.05-11.52), respectively. Of the 32 projects, 17 reported zero seroconversions, 9 had a 0.1-1.5/100 person-year seroconversion rate, and 6 had a >1.5/100 person-year seroconversion rate.
Risk groups or risk factors	Subjects with poor treatment compliance.
Preventability	The prophylactic effectiveness of Truvada is strongly correlated with adherence to the daily dosing regimen. In the iPrEx Study, the odds of HIV-1 acquisition were lower by a factor of 12.9 among subjects with detectable blood levels of FTC and TFV, as compared to those without detectable levels, corresponding to a greater reduction in the risk of HIV-1 acquisition in subjects with quantifiable drug levels. The additional risk minimization measure for this safety concern is further described in Section Part II: Module SV, Table Part V.2.
Impact on the benefit-risk balance of the product	The use of Truvada for a PrEP indication may not always prevent HIV-1 acquisition.
Public health impact	The use of Truvada for a PrEP indication may not always prevent HIV-1 acquisition.

Table SVII.3. Development of Resistance in Patients with Unrecognized or Acute HIV-1 Infection (PrEP Indication) (TVD)

Important Identified Risk:	Development of resistance in patients with unrecognized or acute HIV-1 infection (PrEP indication)
Potential mechanisms	HIV-1 resistant variants may emerge in individuals with unrecognized HIV-1 infection who are taking Truvada for a PrEP indication to reduce the risk of acquiring HIV-1 because while Truvada has activity against HIV-1, Truvada alone does not constitute a complete treatment regimen for HIV-1. The M184V/I and K65R amino acid substitutions in HIV-1 reverse transcriptase are the expected resistance substitutions associated with FTC and TDF, respectively.
Evidence source and strength of evidence	Development of resistance in patients with unrecognized or acute HIV-1 infection has been reported infrequently during the use of Truvada for the PrEP indication in clinical trials, in the postmarketing setting and in the literature.
Characterisation of the risk	In the iPrEx Study, no amino acid substitutions associated with resistance to emtricitabine or tenofovir were detected at the time of seroconversion among 36 subjects in the Truvada group and 64 subjects in the placebo group who became infected with HIV-1 during the trial. Ten subjects were observed to be infected at time of enrollment. The M184V/I substitutions associated with resistance to emtricitabine were observed in 3 of the 10 subjects (2 of 2 in the Truvada group and 1 of 8 in the placebo group). One of the two subjects in the Truvada group harbored wild type virus at enrollment and developed the M184V substitution 4 weeks after enrollment. The other subject had indeterminate resistance at enrollment but was found to have the M184I substitution 4 weeks after enrollment. Comprehensive viral drug resistance testing and drug exposure measurements in iPrEx seroconverters in a clinical trial setting was performed. Clinical genotype and phenotype assays were performed to detect resistance in viral populations. Minor variant FTC/TDF-selected mutations were quantified by deep sequencing and a novel allele-specific polymerase chain reaction (AS-PCR)–based assay that controls for target sequence polymorphisms and yields improved performance when testing isolates from diverse geographic locations. Drug resistance was rare in iPrEx on-study FTC/TDF-randomized seroconverters, and only as low frequency minor variants. FTC resistance among those initiating PrEP with acute infection waned rapidly after drug discontinuation. None of the 82 subjects who acquired HIV-1 after randomization in the Partners PrEP Study developed HIV-1 with the K65R or M184V mutations. Among the 8 partner subjects in the Viread and Truvada study drug groups who were subsequently determined to be infected at randomization based on positive RNA PCR from the enrollment specimens, 2 partner subjects developed HIV-1 infection with resistance to study medications, including 1 partner subject in the Viread group with TDF-resistant virus (K65R mutation) and 1 partner subject in the Truvada group with FTC-resistant virus (M184V mutation). Highly sensitive resistance testing was performed among HIV seroconverters within the Partners PrEP Study. The results suggest that resistance selected by PrEP is rare but can occur both with PrEP initiation during acute seronegative HIV infection and in PrEP breakthrough

Important Identified Risk:	Development of resistance in patients with unrecognized or acute HIV-1 infection (PrEP indication)
	infections and that FTC is associated with a greater frequency of resistance mutations than TDF. Among the 4 adolescents who seroconverted during Study ATN 110 (N=200; age range 18-22 years), no antiretroviral drug resistance was detected {Hosek 2017b}. No genotypic mutations conferring resistance to tenofovir or FTC were detected in the 3 individuals who seroconverted during Study ATN 113 (N=78; age range 15-18 years) {Hosek 2017a}.
Risk groups or risk factors	Subjects with undiagnosed HIV-1 on Truvada for PrEP.
Preventability	Truvada should only be used to reduce the risk of acquiring HIV-1 in individuals confirmed to be HIV-negative prior to initiating Truvada for pre-exposure prophylaxis and re-confirmed at frequent intervals. The additional risk minimization measure for this safety concern is further described in Section Part II: Module SV, Table Part V.2.
Impact on the benefit-risk balance of the product	Resistance mutations reduce susceptibility to emtricitabine and tenofovir DF, as well as to some of the other nucleoside reverse transcriptase inhibitors, and thus reduce some of the future treatment options for optimum suppressive therapy against HIV-1.
Public health impact	Minimal, taking into account the anticipated incidence of this event.

SVII.3.1.2. Important Potential Risks

There are no important potential risks for Truvada or its components.

SVII.3.2. Presentation of the Missing Information

There is no missing information for Truvada or its components.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1. Summary of Safety Concerns

Important Identified Risks	HIV-1 acquisition, including infection resulting from non-adherence (PrEP indication) (TVD)
	Development of resistance in patients with unrecognized or acute HIV-1 infection (PrEP indication) (TVD)
Important Potential Risks	None
Missing Information	None

PART III: PHARMACOVIGILANCE PLAN

III.1. Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond ADRs Reporting and Signal Detection:

Specific Adverse Reaction Follow-up Questionnaires

Specific targeted follow-up questionnaires are used to obtain comprehensive information for the reported adverse events (Table Part III.1). A copy of the follow-up questionnaires is provided in Annex 4.

Table Part III.1. Specific Adverse Reaction Follow-up Questionnaires

Name of Questionnaire	Description
Lack of efficacy in pre-exposure prophylaxis	The questionnaire is designed to collect information on causes of seroconversion and HIV-1 resistance mutations in patients who seroconvert when using Truvada for PrEP.

Other Forms of Routine Pharmacovigilance Activities

There are no other forms of routine pharmacovigilance activities for any of the safety concerns.

III.2. Additional Pharmacovigilance activities

Table Part III.2. Ongoing and Planned Additional Pharmacovigilance Activities

Study title	Rationale and Study Objectives	Study Design and Study Populations	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

III.3. Summary Table of additional Pharmacovigilance activities

Table Part III.3. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

PART IV:
PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing postauthorization efficacy studies for Truvada.

PART V:
RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1. ROUTINE RISK MINIMIZATION MEASURES

The routine risk minimization measure for Truvada in the EU comprise of the SmPC, the package leaflet (PL), and the legal status of the product. Truvada is subject to restricted medical prescription, whereby therapy should be initiated by a physician experienced in the management of HIV infection (SmPC Section 4.2).

The routine risk minimization recommendations provided by the SmPC and PL are described further by safety concern in Table Part V.1.The legal status can be considered a general measure applicable to all individual safety concerns.

Table Part V.1. Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk minimization activities
Important Identified Risks	
HIV-1 Acquisition, including infection resulting from non-adherence (TVD – PrEP)	Routine risk communication: SmPC Section 4.4 PL Sections: 2 and 3 Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.4: Warning that HIV-1 uninfected individuals should be counselled at frequent intervals to strictly adhere to the recommended Truvada daily dosing schedule.
Development of resistance in patients with unrecognized or acute HIV-1 infection (TVD – PrEP)	Routine risk communication: SmPC Sections 4.3 and 4.4 PL Section: 2 Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.4: Warning on confirming individuals to be HIV-negative prior to initiating Truvada and at frequent intervals (e.g, at least every 3 months) while taking Truvada for PrEP.
Important Potential Risks	
None	
Missing Information	
None	

V.2. Additional Risk minimization measures

Table Part V.2. Additional Risk Minimization: PrEP educational materials

Education program directed to prescribers (As part of this program, the following specific PrEP educational risk minimization materials will be made available: Checklist for prescribers, Educational brochure for prescribers, Educational brochure for the individual at risk and Reminder card, to act as reminder to users to adhere to the dosing schedule and attend scheduled clinical visits.)	
Objective(s)	The PrEP educational materials are designed to manage the risks of HIV-1 acquisition, including infection resulting from non-adherence, and development of resistance in patients with unrecognized or acute HIV-1 infection.
Rationale for the additional risk minimization activity	Prescriber and individual awareness on the appropriate use of Truvada for PrEP will assist in minimizing the risk of HIV-1 Acquisition, including infection resulting from non-adherence, and the risk of development of resistance in patients with unrecognized or acute HIV-1 infection.
Target audience and planned distribution path	The PrEP educational materials have been distributed to the healthcare professionals who are likely to prescribe Truvada for PrEP, namely infectious disease, sexual health, genitourinary medicine and HIV physicians. If other groups of prescribers are identified, an additional distribution will be made. Additionally, educational materials are available to be sent to healthcare providers upon request.
Plans to evaluate the effectiveness of the interventions and criteria for success	A cross-sectional survey (GS-EU-276-4027) was conducted to assess the effectiveness of the prescriber's level of awareness of risk minimization measures and appropriate use and risks associated with Truvada for the PrEP indication. The study report was submitted in November 2018 (procedure number EMEA/H/C/000594/II/0159, date of approval 14 Feb 2019 [CHMP Opinion]).
Rationale for proposing to remove additional risk minimization measure(s)	Not applicable

Table Part V.3. Additional Risk Minimization Activity for Important Identified Risk of Renal Toxicity

Healthcare Professional Educational Initiatives (comprised of: HIV educational guide for prescribers of Truvada to pediatric patients); Truvada for PrEP educational guide for prescribers, which include renal education statements	
Objective(s)	To minimize the risk of renal toxicity associated with TDF component of Truvada by communicating to prescribers important renal management information primarily on assessing renal function at baseline and during therapy, the dosage adjustment requirements for patients with pre-existing renal impairment and when to give consideration to interrupting TDF treatment in the presence of a decline in renal function. [Note: the HCP educational guides specific to the use of TDF in HIV-1 pediatric patients have been prepared to provide advice to physicians on the management of renal effects in pediatric patients. The guides also include additional information specific to use of TDF in pediatric patients on the approved indications, the management of bone effects, and information on the appropriate dosing of TDF in pediatric patients]
Rationale for the additional risk minimization activity	Prescriber awareness of important renal management information will assist in preventing or minimizing the risk of renal toxicity.
Target audience and planned distribution path	Prescribers of Truvada to pediatric patients (HIV-1 indication and PrEP indication) via mail.

Healthcare Professional Educational Initiatives (comprised of: HIV educational guide for prescribers of Truvada to pediatric patients); Truvada for PrEP educational guide for prescribers, which include renal education statements	
Plans to evaluate the effectiveness of the interventions and criteria for success	Drug Utilization Studies An observational, drug utilization study of Viread in children and adolescents with HIV-1 infection (GS-EU-104-0433) was conducted to assess the effectiveness of the risk minimization measures (EU SmPC and HIV pediatric educational guide) that have been implemented post-approval of Viread in the pediatric population. The clinical study report was submitted in December 2017 (procedure number EMEA/H/C/WS1326, date of approval 17 May 2018 [CHMP Opinion]). A cross-sectional survey (GS-EU-276-4027) was conducted to collect information on the effectiveness of risk minimization measures in subjects receiving Truvada for PrEP The clinical study report was submitted in November 2018 (procedure number EMEA/H/C/000594/II/0159, date of approval 14 Feb 2019 [CHMP Opinion]).
Rationale for proposing to remove additional risk minimization measure(s)	The MAH proposes to remove the additional risk minimization measures for pediatric patients (HIV educational guide) based upon the following: • The drug utilization study conducted to evaluate the effectiveness of risk minimization measures including the pediatric educational guides has been completed; the final GS-EU-104-0433 study report was submitted on 21 December 2017. • Truvada has been approved for use in the pediatric HIV infected population 12 to <18 years of age since 2017 and the PrEP pediatric population 12 to <18 years of age since 2018. The safety profile of TDF/FTC in the pediatric population is monitored through routine pharmacovigilance activities and reported in the Truvada PSUR/PBRERs, with no new safety concerns identified. • There has not been any evidence to support an increase in the frequency or severity of renal adverse events in the pediatric population reported for TDF/FTC in the EU since the approval in the HIV and PrEP pediatric populations. • Long-term data in the pediatric populations are available up to Week 192. No new safety concerns were identified from these long-term data. There are no further studies ongoing within the pediatric population. • Renal messages are included in the European treatment guidelines for HIV infection {European AIDS Clinical Society (EACS) 2020a} {Bamford 2015} and the renal monitoring recommendations are provided in the EU SmPCs for Truvada. Given that renal toxicity risk minimization measures in both pediatrics and adults have become fully integrated into standard clinical practice (through inclusion in treatment guidelines), the risk is considered to be fully characterized and appropriately managed. Taking these points together, and, given the well-known safety profile of FTC/TDF, the MAH considers that the renal safety concerns in HIV-1 infected pediatric population can be managed through routine risk minimization activities. Nevertheless, the renal education statements included in Truvada for PrEP educational guide for prescribers will remain, as the aRMMs for the PrEP indication will remain in the RMP and Annex IID of Truvada.

V.3. Summary of risk minimization measures

Truvada has the legal status of medicinal product subject to restricted medical prescription in the EU, whereby therapy should be initiated by a physician experienced in the management of HIV infection [SmPC section 4.2]. This routine risk minimization measure beyond the product information can be considered a general measure applicable to all of the safety concerns summarized below.

Table Part V.4. Summary Table of Pharmacovigilance and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important identified risk(s)		
HIV-1 Acquisition, including infection resulting from non-adherence (TVD – PrEP)	Routine risk minimization measure: SmPC Section 4.4 PL Sections: 2 and 3 Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.4: Warning that HIV-1 uninfected individuals should be counselled at frequent intervals to strictly adhere to the recommended Truvada daily dosing schedule. Additional risk minimization measures: Education program for prescribers to help them educate individuals at high risk of acquiring HIV-1 infection.	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Targeted follow-up questionnaire for lack of efficacy, seroconversion and/or resistance mutation(s). Additional pharmacovigilance activities: None.
Development of resistance in patients with unrecognized or acute HIV-1 infection (TVD – PrEP)	Routine risk minimization measure: SmPC Sections 4.3 and 4.4 PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.4: Warning on confirming individuals to be HIV-negative prior to initiating Truvada and at frequent intervals (e.g, at least every 3 months) while taking Truvada for PrEP. Additional risk minimization measures: Education program for prescribers to help them educate individuals at high risk of acquiring HIV-1 infection.	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Targeted follow-up questionnaire for lack of efficacy, seroconversion and/or resistance mutation(s). Additional pharmacovigilance activities: None.
Important potential risk(s)		
None		
Missing information		
None		

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

I. SUMMARY of risk management plan for truvada (emtricitabine/tenofovir df)

This is a summary of the risk management plan (RMP) for Truvada. The RMP details important risks of Truvada, how these risks can be minimized, and how more information will be obtained about Truvada's risks and uncertainties (missing information).

Truvada's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Truvada should be used.

This summary of the RMP for Truvada should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of the Truvada RMP.

II. The Medicine and What is it Used for

Truvada is authorized in antiretroviral combination therapy for the treatment of human immunodeficiency virus type 1 (HIV-1) infected adults, and for the treatment of HIV-1 infected adolescents with nucleoside reverse transcriptase inhibitor (NRTI) resistance or toxicities precluding the use of first line agents. Truvada is also indicated in combination with safer sex practices for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in adults and adolescents at high risk (see SmPC for the full indication). It contains emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) as the active substance and it is given orally.

Further information about the evaluation of Truvada's benefits can be found in Truvada's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000594/human_med_001113.jsp&mid=WC0b01ac058001d124

III. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Truvada, together with measures to minimize such risks and the proposed studies for learning more about Truvada's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;

- Important advice on the medicine's packaging;

- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimizes its risks.

Together, these measures constitute routine risk minimization measures.

In the case of Truvada, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Truvada is not yet available, it is listed under 'missing information' below.

III.A. List of Important Risks and Missing Information

Important risks of Truvada are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Truvada. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table Part VI.1. List of Important Risks and Missing Information

Important Identified Risks	HIV-1 acquisition, including infection resulting from non-adherence (pre-exposure prophylaxis [PrEP] indication) (Truvada, TVD)
	Development of resistance in patients with unrecognized or acute HIV-1 infection (PrEP indication) (TVD)
Important Potential Risks	None
Missing Information	None

III.B. Summary of Important Risks

Table Part VI.2. Summary of Important Risk(s) and Missing Information

Important Identified Risk	**HIV-1 Acquisition, Including Infection Resulting From Non-adherence (PrEP Indication)**
Evidence for linking the risk to the medicine	HIV-1 acquisition has been reported infrequently with the use of Truvada for the PrEP indication in clinical trials, in the postmarketing setting and in the literature, and has been associated with poor adherence.
Risk factors and risk groups	Subjects with poor treatment compliance.
Risk Minimization Measure(s)	Routine risk minimization measure: SmPC Section 4.4 PL Sections: 2 and 3 Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.4: Warning that HIV-1 uninfected individuals should be counselled at frequent intervals to strictly adhere to the recommended Truvada daily dosing schedule. Additional risk minimization measures: Truvada for PrEP indication education program for prescribers.
Additional Pharmacovigilance activities	None.
Important Identified Risk	**Development of Resistance in Patients with Unrecognized or Acute HIV-1 Infection (PrEP Indication)**
Evidence for linking the risk to the medicine	Development of resistance in patients with unrecognized or acute HIV-1 infection has been reported infrequently during the use of Truvada for the PrEP indication in clinical trials, in the postmarketing setting and in the literature.
Risk factors and risk groups	Subjects with undiagnosed HIV-1 on Truvada for PrEP.
Risk Minimization Measure(s)	Routine risk minimization measure: SmPC Sections 4.3 and 4.4 PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.4: Warning on confirming individuals to be HIV-negative prior to initiating Truvada and at frequent intervals (e.g, at least every 3 months) while taking Truvada for PrEP. Additional risk minimization measures: Truvada for PrEP indication education program for prescribers.
Additional Pharmacovigilance activities	None.

III.C. Postauthorization Development Plan

III.C.1. Studies which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Truvada.

III.C.2. Other Studies in PostAuthorization Development Plan

There are no other studies required for Truvada.

PART VII: ANNEXES

Table of Contents

Annex 1. EudraVigilance Interface

This XML file is submitted electronically and can be provided on request.

Annex 2. Tabulation Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program

Annex 3. Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

Lack of efficacy in pre-exposure prophylaxis

Annex 5. Protocols for Proposed and Ongoing Studies in RMP Part IV

None

Annex 6. Details of Proposed Additional Risk Minimization Measures (if applicable)

Annex 7. Other Supporting Data (Including Referenced Material)

The following information is included in this annex:

- Referenced material (Refer to REFERENCES)

Annex 8. Summary of Changes to the Risk Management Plan over Time

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Annex 4. Specific Adverse Drug Reaction Follow-up Forms

The following information is included in this annex:

- Lack of efficacy in pre-exposure prophylaxis questionnaire

GILEAD	***TVD PrEP Lack of Efficacy, Seroconversion and/or Resistance Mutation(s) Targeted Questionnaire***

Patient initials:	DOB:	MCN#:

1. Please provide the start date of Truvada for PrEP (DAY/MONTH/YEAR):
2. Please provide Truvada lot number, if available: ☐ N/A
   Are any of the Truvada tablets available for analysis? ☐ YES (if yes, we may contact you) ☐ NO
3. Was the individual tested for HIV prior to starting Truvada PrEP?
   ☐NO
   ☐YES DATE (DAY/MONTH/YEAR): / / Type of HIV test used:
   Result: Antigen ☐ POSITIVE ☐ NEGATIVE ☐ RESULT NOT AVAILABLE
   Antibody ☐ POSITIVE ☐ NEGATIVE ☐ RESULT NOT AVAILABLE
4. Was the individual's HBV status confirmed before starting Truvada?
   ☐YES Result:
   ☐NO
5. What was the individual's sex at birth?
   ☐ MALE
   ☐ FEMALE
6. What is the individual's gender identity?
   ☐ MALE
   ☐ FEMALE
7. What is the individual's sexual behavior pattern?
   ☐ MAN WHO HAS SEX WITH MEN
   ☐ TRANSGENDER WOMAN WHO HAS SEX WITH MEN
   ☐ MAN WHO HAS SEX WITH WOMEN
   ☐ WOMAN WHO HAS SEX WITH MEN
   ☐ WOMAN WHO HAS SEX WITH WOMEN
   ☐ OTHER, PLEASE SPECIFY:_____
8. What was the reason for prescribing PrEP (check all that apply)?
   ☐ INCONSISTENT OR NO CONDOM USE
   ☐ UNSAFE INTRAVENOUS DRUG USE
   ☐ PARTNER IS INFECTED WITH HIV
   ☐ EXCHANGE OF SEX FOR COMMODITIES (SUCH AS MONEY, FOOD, OR SHELTER)
   ☐ PARTNER/ MULTIPLE PARTNERS KNOWN TO BE FROM A HIGH HIV PREVALENCE AREA OR SOCIAL NETWORK
   ☐ SEX UNDER THE USE OF RECREATIONAL DRUGS (CHEMSEX)
   ☐ OTHER (PLEASE SPECIFY):_____
9. Was the individual prescribed Truvada once-daily?
   ☐YES
   ☐NO IF NOT, WHAT WAS THE REASON?. _____
   _____
10. Was the individual counselled about safe sex practices?
    ☐YES
    ☐NO
11. Was the individual practicing safe sex before the reported HIV seroconversion, including using condoms consistently and correctly?
    ☐YES
    ☐NO

12. How frequently was the individual's HIV status tested?

☐ EVERY MONTH

☐ EVERY 3 MONTHS

☐ LESS FREQUENTLY THAN EVERY 3 MONTHS

☐ OTHER, PLEASE SPECIFY:_____

Please provide the HIV test results in the table below.

13. Please complete the following table and/or attach lab printouts if unable to fit on chart:

DATE (DAY/MONTH/YEAR)	HIV STATUS TEST RESULT	GENOTYPE / PHENOTYPE TESTING RESULT
PRIOR TO INITIATING TRUVADA PREP		
WHILE TAKING TRUVADA PREP (PRIOR TO REPORTED HIV SEROCONVERSION)		
AT TIME OF REPORTED HIV SEROCONVERSION, AND SUBSEQUENTLY		

14. For patients with resistance mutation(s), was the mutation(s):

☐ ACQUIRED DURING TRUVADA FOR PREP USE. PLEASE SPECIFY CLINICAL REASONING:

_____

_____

☐ TRANSMITTED PLEASE SPECIFY CLINICAL REASONING:

_____

_____

☐ UNKNOWN

15. Was the individual tested for other sexually transmitted infections (e.g. gonorrhoea, chlamydia, HPV)?

☐ NO

☐ YES Which STIs was the individual tested for? PLEASE SPECIFY: _____

_____

How frequently was the individual tested?

☐ EVERY MONTH

☐ EVERY 3 MONTHS

☐ LESS FREQUENTLY THAN EVERY 3 MONTHS

☐ OTHER, PLEASE SPECIFY:_____

16. Was the individual adherent to Truvada PrEP as prescribed? ☐YES ☐NO

If no, please estimate the individual's degree of non-adherence with treatment:

The individual missed on average _____ doses per week and missed an average of _____ doses per month

What was the reason the individual missed doses/didn't adhere to the prescribing dosing schedule?

☐ THE INDIVIDUAL WASN'T WILLING TO TAKE TRUVADA DAILY. WHAT WAS THE REASON?_____

_____

☐ THE INDIVIDUAL DECIDED TO STOP TAKING TRUVADA WHEN? (DAY/MONTH/YEAR) / /

WHAT WAS THE REASON?_____

_____

☐ THE INDIVIDUAL FORGOT TO TAKE TRUVADA

☐ THE INDIVIDUAL WAS EXPERIENCING SIDE EFFECTS TO TRUVADA WHAT WAS THE SIDE EFFECT?_____

_____

☐ THE INDIVIDUAL DIDN'T GET A REFILL ON TIME

☐ THE INDIVIDUAL LOST THE MEDICATION

☐ THE INDIVIDUAL DIDN'T WANT OTHERS TO KNOW HE/SHE WAS TAKING TRUVADA FOR PREP

☐ THE INDIVIDUAL EXPERIENCED/WAS AWARE OF NEGATIVE REACTIONS OR OPINIONS WITH REGARDS TO PREP USE (E.G. VERBAL ABUSE/COMMENTS)

☐ OTHER, PLEASE SPECIFY: _____

_____

17. Was Truvada PrEP stopped after HIV seroconversion was confirmed?

☐YES Please provide stop date (DAY/MONTH/YEAR): / /

☐NO Please list any other anti-retroviral therapies that were initiated after seroconversion:

_____

_____

18. Please specify the individual's concomitant medications (including any herbal therapy):

(☐NONE ☐UNKNOWN)

_____

_____

Please be aware that information provided to Gilead relating to you, may be used to comply with applicable laws and regulations. Gilead processes your personal or sensitive data in accordance with applicable data protection laws and the Gilead Privacy Statement, available to you either on www.gilead.com/privacy or upon request.

Annex 6. Details of Proposed Additional Risk Minimization Measures

Approved Key messages of the additional risk minimization measures

TRUVADA PREP RISK MINIMIZATION ACTIVITIES

Key messages that are included in the PrEP educational materials, are as follows:

- The importance of strict adherence to the recommended dosing regimen
- That Truvada for PrEP should be part of an overall HIV-1 infection prevention strategy
- The importance of regular monitoring of HIV-1 serostatus to avoid continuing to take Truvada for a PrEP indication if seroconversion has occurred to reduce the risk of development of resistant HIV-1 variants
- That Truvada should not be used in uninfected adults with an estimated creatinine clearance (CrCl) below 60 mL/min and should only be used in individuals with CrCl below 80 mL/min if the potential benefits are considered to outweigh the potential risks
- That Truvada is not recommended in uninfected adolescents with renal impairment
- That renal function should be regularly monitored in all individuals