NON-INTERVENTIONAL (NI) STUDY REPORT

PASS information

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Research question and objectives	The objective of this study is to determine healthcare providers' level of awareness of risk minimisation materials and appropriate use and risks associated with Truvada for PrEP

Country(-ies) of study	France, Germany, Ireland, Netherlands, Norway, United Kingdom
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A Cross-Sectional Post-authorisation Safety Study to Assess Healthcare Providers' Level of Awareness of Risk Minimisation Materials for Truvada® for Pre-Exposure Prophylaxis in the European Union

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse Event
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
EC	Ethics Committee
EDC	Electronic Data Capture
EU	European Union
GVP	Good Pharmacovigilance Practice
HCP	Healthcare Professional
HIV-1	Human Immunodeficiency Virus-1
MD	Missing Data
PAS	Post-authorisation Study
PASS	Post-authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
PrEP	Pre-Exposure Prophylaxis
PVE	Pharmacovigilance and Epidemiology
QPPV	Qualified Person Responsible for Pharmacovigilance
RMM	Risk Minimisation Materials
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedures
UK	United Kingdom

1. ABSTRACT

Title: A Cross-Sectional Post-authorisation Safety Study to Assess Healthcare Providers' Level of Awareness of Risk Minimisation Materials for Truvada® for Pre-Exposure Prophylaxis in the European Union

Keywords: Truvada; human immunodeficiency Virus-1; risk minimisation; survey

Rationale and background: Truvada for Pre-Exposure Prophylaxis (PrEP) in combination with safer sex practice was approved to reduce the risk of sexually acquired human immunodeficiency virus-1 (HIV-1) infection in adults at high risk. Additional risk minimisation measures (RMMs) for the use of Truvada for PrEP are included in the Truvada European Union (EU) Risk Management Plan (RMP). This survey was implemented to assess the level of awareness of the healthcare professional (HCP)-directed RMMs, as well as guidance in the Summary of Product Characteristics (SmPC), in educating HCPs on the appropriate use and risks of Truvada for a PrEP indication.

Research question and objectives: The objective of this study was to determine HCPs' level of awareness of risk minimisation materials and appropriate use and risks associated with Truvada for PrEP.

Study design: Cross-sectional study.

Setting: A convenience sample of HCPs from France, Germany, Ireland, the Netherlands, Norway, and the United Kingdom (UK) recruited from the same population of HCPs that were targeted for the distribution of the Truvada for PrEP RMMs as agreed with the national competent authorities. The target population represented practice specialities which are considered likely to prescribe Truvada for PrEP.

Subjects and study size, including dropouts: To be eligible, HCPs must have agreed to take part in the study. HCPs who participated in the cognitive pre-test of the survey were ineligible to participate in the study. The sample size of 200 completed HCP surveys was determined based on statistical considerations. A total of 4063 invitations were sent to HCPs; 301 responded and agreed to participate in the study, giving an overall response rate of 7.4% (301/4063). There were 290 HCPs who met the study eligibility requirements and completed all questions about the appropriate use and risks for Truvada for PrEP; these 290 HCPs comprised the primary analysis set.

Variables and data sources: The survey questionnaire for HCPs was developed to assess the awareness of the RMMs for Truvada for PrEP, awareness about the appropriate use and risks associated with Truvada for PrEP, and brief demographic information of the HCPs.

Statistical methods: All analyses were descriptive and were conducted using SAS® version 9.4 or above. Qualitative variables were described by the absolute and relative (%) frequency of each category and number of missing data. Two-sided 95% confidence intervals (CI) for proportions were calculated for the effectiveness endpoints using exact methods. All analyses were

performed overall and by country. Analyses of the effectiveness endpoints were also performed stratified by medical speciality, receipt of the Truvada for PrEP additional RMMs, and prescribed Truvada for PrEP. The majority of respondents (61.8%) were either HIV (32.1%) or infectious disease specialists (29.7%). Only two-fifths of respondents had written a prescription for Truvada for PrEP (39.7%).

Results: Approximately two-thirds of respondents were doctors/physicians (69.0%) and almost half of HCPs (42.7%) practised in a hospital setting (either a teaching, academic, or university hospital setting or a general/district hospital) while nearly one-third practised in an HIV clinic (29.0%).

Knowledge levels were assessed for 5 key aspects of the appropriate use of Truvada for PrEP. Nearly all HCPs (98.6%) knew that HIV-1 uninfected individuals should be counseled to adhere to the recommending dosing schedule for Truvada for PrEP. The majority of HCPs knew Truvada for PrEP cannot be initiated in an individual who has signs and symptoms of an acute HIV infection while waiting for laboratory results, HIV-1 uninfected individuals should be screened for Hepatitis B before starting Truvada for PrEP, and Truvada for PrEP should only be used as part of a comprehensive prevention strategy because Truvada for PrEP is not always effective in preventing the acquisition of HIV-1 (86.2%, 85.5%, and 77.2%, respectively). Over half of HCPs knew that HIV-1 resistance mutations have been reported in individuals with undiagnosed HIV-1 infection while taking only Truvada (57.6%). Most HCPs knew the recommended dosing regimen for Truvada for PrEP (87.6%). Results for knowledge levels were generally similar between countries.

Generally, knowledge levels were similar between specialities. However, in comparison with HCPs who had infectious disease/HIV or genitourinary medicine/venereal disease/urology specialities, fewer general practice/internal medicine specialists (70.6%) and other specialities including emergency medicine (75.0%) knew Truvada for PrEP cannot be initiated in individuals who have signs and symptoms of an acute HIV infection while waiting for laboratory results. Additionally, HCPs with “other” specialities including emergency medicine had lower knowledge levels of the recommended dosing regimen for Truvada for PrEP (75.0%) in comparison with the rest of the HCP specialities.

For all effectiveness endpoints, knowledge levels were higher among HCPs that received the Truvada for PrEP additional RMMs compared with those that did not receive or did not remember receiving the additional RMMs. In general, knowledge levels of HCPs who prescribed Truvada for PrEP did not differ from those who did not prescribe Truvada for PrEP.

For the majority of all other questions on the appropriate use and risks associated with the use of Truvada for PrEP, knowledge levels were over 80%. Only knowledge of the estimated creatinine clearance below which Truvada for PrEP is not recommended per the Truvada SmPC, and acknowledgement of receipt of each of the 4 items in the RMM packet, were below 50% (49.0% and 42.5%, respectively).

Discussion and conclusions: The primary effectiveness endpoint was comprised of 6 items. Five of the items were key aspects regarding the appropriate use of Truvada for PrEP and the sixth item was knowledge of the recommended dosing regimen for Truvada for PrEP. For the primary endpoint, knowledge levels for 4 of these 6 items met the pre-specified threshold of 80% or higher. The majority of HCPs knew the recommended dosing regimen for Truvada PrEP (87.6%) and nearly all HCPs (98.6%) knew that HIV-1 uninfected individuals should be counselled to adhere to the recommending dosing schedule for Truvada for PrEP. The majority of HCPs knew Truvada for PrEP cannot be initiated in an individual who has signs and symptoms of an acute HIV infection while waiting for laboratory results (86.2%), HIV-1 uninfected individuals should be screened for Hepatitis B before starting Truvada for PrEP (85.5%), and Truvada for PrEP should only be used as part of a comprehensive prevention strategy because Truvada for PrEP is not always effective in preventing the acquisition of HIV-1 (77.2%). While over half of HCPs knew that HIV-1 resistance mutations have been reported in individuals with undiagnosed HIV-1 infection while taking only Truvada (57.6%), knowledge levels for this endpoint may have been lower because HIV-1 resistance mutations are not common.

Results for knowledge levels were generally similar across countries and HCP specialities. Knowledge rates tended to be higher for specialities more likely to see individuals at high risk of sexually acquiring HIV-1 infection (e.g., infectious disease/HIV specialists and genitourinary medicine/venereal disease/urology specialists).

In this study, knowledge levels of all effectiveness endpoints were higher among HCPs that received the Truvada for PrEP additional RMMs compared to those that did not receive or do not remember receiving the additional RMMs, suggesting the Truvada for PrEP RMMs are useful.

For the survey questions which were not part of the primary analysis, knowledge levels were 80% or higher for the majority of items. Only 1 question had knowledge levels less than 50%, the estimated creatinine clearance below which Truvada for PrEP is not recommended per the Truvada SmPC (49.0%). Additionally, less than half of HCP respondents acknowledged receipt of all 4 items included in the RMM packet (42.5%)

Several study limitations should be noted. The primary limitation of this cross-sectional study was selection bias due to use of a convenience sample. For this study, country selection was carefully considered to obtain a feasible yet diverse European sample by including countries from various regions of Europe where Truvada for PrEP is commercialised and incidence of HIV-1 infection are higher. Despite significant effort to increase the number of respondents in countries with low numbers of HCPs to recruit, although response rates for Ireland and Norway were not poor (32.6% and 4.5%, respectively), the number of respondents especially for Norway was low (n=2). However, since the target audience invited to participate in this survey matched the target audience for the distribution of the additional RMM, and the number of respondents was proportional to the number available to be invited, the impact of selection bias on the overall survey results is probably small.

Another limitation is that the study relied on self-reporting. It is possible that HCPs may have inaccurately reported the information due to either recall bias or social desirability bias. Since this survey was conducted close to the time that the Truvada for PrEP RMMs were disseminated (within a year), the impact of recall bias may be minimal.

The objective of this study was to evaluate the effectiveness of the Truvada for PrEP additional RMMs. However, information contained in these materials is also included in the SmPC. Therefore, it is challenging to separate the effectiveness of these materials from that of the SmPC.

The results of this study indicate that the majority of HCPs recalled receiving the Truvada for PrEP RMMs. Overall, knowledge levels of appropriate use of, and risks associated with, Truvada for PrEP were high, with the majority of HCPs having 80% or greater knowledge of the information included in the Truvada for PrEP RMMs. Additionally, HCPs who recalled receiving the Truvada for PrEP RMMs had higher knowledge of the information in comparison with HCPs who did not recall receiving these materials.

Based on the results of this study, it appears that the Truvada for PrEP RMMs are effective in educating and informing HCPs of the appropriate use of, and risks associated with, Truvada for PrEP.

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