Current PrEP (TVD/TDF) Phase 3b/4 Studies and REMS update

Jim Rooney

Gilead Sciences

Ongoing and Planned Phase 3/4 Research, Including Demonstration Projects

- Phase 3 studies are continuing to evaluate PrEP in various demographic groups
- Gilead is committed to post-marketing demonstration studies in the U.S. and globally
- Collaborators: ANRS, CDC, FHI, MRC, NIAID (DAIDS), NICHD (ATN), SFDPH, U. Washington, and Gilead Sciences

Population	Studies	Participants
MSM	**17**	**13,920**
Heterosexual Men & Women Serodiscordant Couples	**10**	**14,630**
Total	**27**	**28,550**

ANRS = French National Agency for AIDS Research; CDC = Centers for Disease Control and Prevention; FHI = Family Health International; MRC = Medical Research Council (UK); NIAID = National Institute of Allergy and Infectious Diseases; DAIDS = Division of AIDS; NICHD = National Institute of Child Health and Human Development; SFDPH = San Francisco Department of Public Health

Phase 3/4 Research and Demonstration Projects in MSM

Study	N	Duration	Location
Ongoing Phase 3 Studies			
IPERGAY	1900	24 months	France, Canada
Demonstration Projects and Open-Label Extensions (planned and ongoing)			
iPrEx OLE	1770	72 weeks	Americas, Thailand, S. Africa
DAIDS PrEP MSM Demo	500	12 months	U.S.
CDC PrEP Demo*	600	12 months	U.S.
PROUD	5000 (500 as pilot)	12 months on tx, 12 month follow-up	U.K.
Project PrEPare 110	200	48 weeks	U.S.
SFDPH EPIC PrEP	300	12 months	U.S.
ALERT	400	12 months+	U.S.
Los Angeles PATH	300	48 weeks	U.S.
Seattle PrEP	300	48 weeks	U.S.
NYC PrEP	200	12 months	U.S.
Brazilian PrEP	400	12 months	Brazil
Rio PrEP	65	12 months	Brazil
HPTN 073	225	12 months	U.S.
HPTN 069**	400	48 weeks	U.S.
HPTN 067**	360	34 weeks	U.S., Thailand, S. Africa
HVTN 505	1000	5 years	U.S.
TOTAL: 17	**13,920**		

*CDC PrEP Demo includes both MSM and heterosexual men and women (1200 participants total)
**Includes both MSM and heterosexual women (estimated 50% MSM, 50% heterosexual women)

Phase 3/4 Research and Demonstration Projects in Heterosexual Women and Men

Study	N	Duration	Location
Ongoing Phase 3 Studies			
Partners PrEP (discordant couples)	4758 couples	12 month extension	Kenya, Uganda
CDC Bangkok TDF (IVDU)	2413	Endpoint driven	Thailand
MTN 003/VOICE (women)	5029	36 months	Uganda, South Africa, Zimbabwe
Demonstration Projects and Open-Label Extensions (planned and ongoing)			
CDC PrEP Demo* (men and women)	600	12 months	U.S.
HPTN 069**	200	48 weeks	U.S.
HPTN 067**	~180	34 weeks	U.S., Thailand, S. Africa
TDF2 Open-Label Extension (men and women)	900 (all rollover)	12 months	Botswana
CHAMPS (men and women)	150	12 months	South Africa
MTN 018/CHOICE (women)	4300 (4000 VOICE rollover)	12 months	Uganda, South Africa, Zimbabwe
UW Partners PrEP Demo (discordant couples)	1000	24 months	Kenya, Uganda
TOTAL: 10	**14,630⁺**		

*CDC PrEP Demo includes both MSM and heterosexual men and women (1200 participants total)
**Includes both MSM and heterosexual women (estimated 50% MSM, 50% heterosexual women)
⁺Excluding rollover participants

Post Marketing Requirements (PMRs) Accrued with Truvada PrEP Approval

- PMR (1906-1) to report data on pregnancy outcomes for women who become pregnant while taking Truvada for PrEP
- PMR (1906-2) to collect and evaluate viral isolates for resistance from 150 individuals participating in demonstration projects of PrEP who acquire HIV while taking Truvada
- PMR (1906-3) to conduct a study in at least 7000 participants in demonstration projects to evaluate drug adherence and its relationship to adverse events, risk of seroconversion, and resistance development in seroconverters

Post Marketing Commitments (PMCs) Accrued with Truvada PrEP Approval

- PMC (1906-4) to provide national drug utilization data in order to better characterize individuals who utilize Truvada for a PrEP indication

- PMC (1906-5) to study adherence in a US CDC Demonstration project of Truvada for a PrEP indication

What is a REMS?

- Risk Evaluation and Mitigation Strategy
- FDA program to manage a known or potential risk associated with a drug
  - Designed to ensure the benefits of a drug outweigh its risks
- Goals of REMS for Truvada for PrEP is to educate prescribers and individuals about
  - The importance of adherence
  - The importance of regular monitoring of HIV-1 serostatus
  - Truvada for PrEP must be part of a comprehensive prevention strategy

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Truvada REMS document. Approved by the FDA on July 16, 2012

REMS Website
www.truvadapreprems.com

- Non-promotional, also links from the commercial educational website
- Supports the goals as defined in the Risk Evaluation and Mitigation Strategy (REMS)
- Emphasizes the need for regular HIV testing, adherence and a comprehensive prevention strategy
- Allows for online training of healthcare providers
- Provides access to all REMS materials

Truvada REMS website. Available at: www.truvadapreprems.com

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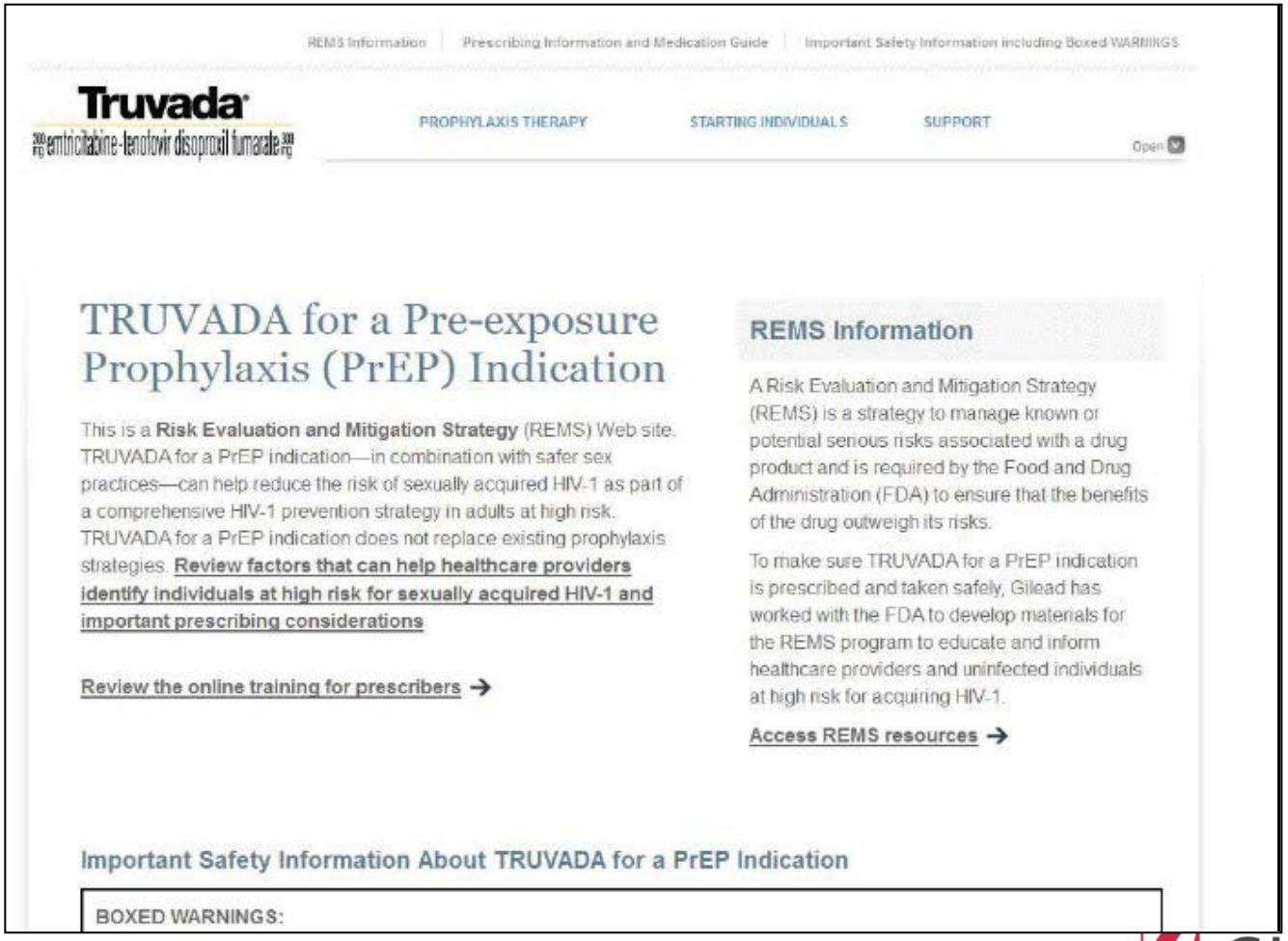
REMS Website (Truvadapreprems.com): Landing Page



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Truvada REMS website. Available at: www.truvadapreprems.com

REMS Materials
Available at www.truvadapreprems.com

- Dear Healthcare Provider Letter
- Training Guide for Healthcare Providers
- Important Safety Information for Healthcare Providers
- Safety Information Fact Sheet
- Agreement Form
- Checklist for Prescribers
- Medication Guide
- Important Safety Information for Uninfected Individuals
- Full Prescribing Information

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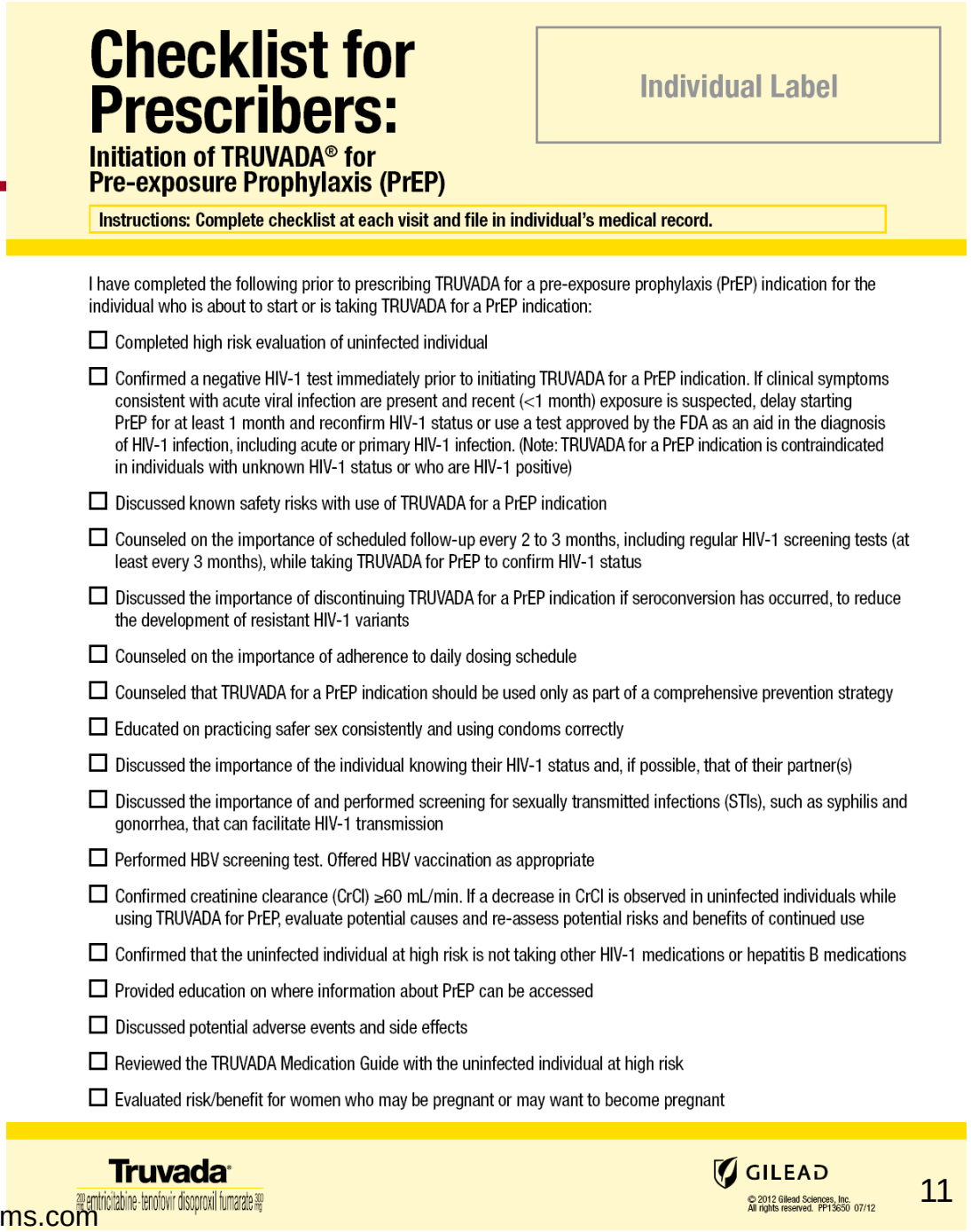
Truvada REMS website. Available at: www.truvadapreprems.com

Checklist for Prescribers:

- Checklist of key components for prescribers to consider before prescribing PrEP
- Checklist items include
  - Confirming a negative HIV-1 test
  - Screening for signs or symptoms of acute HIV infection
  - Counselling on safety risks
  - Importance of adherence



Checklist for Prescribers:

Initiation of TRUVADA® for Pre-exposure Prophylaxis (PrEP)

Individual Label

Instructions: Complete checklist at each visit and file in individual's medical record.

I have completed the following prior to prescribing TRUVADA for a pre-exposure prophylaxis (PrEP) indication for the individual who is about to start or is taking TRUVADA for a PrEP indication:

- ☐ Completed high risk evaluation of uninfected individual
- ☐ Confirmed a negative HIV-1 test immediately prior to initiating TRUVADA for a PrEP indication. If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposure is suspected, delay starting PrEP for at least 1 month and reconfirm HIV-1 status or use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection. (Note: TRUVADA for a PrEP indication is contraindicated in individuals with unknown HIV-1 status or who are HIV-1 positive)
- ☐ Discussed known safety risks with use of TRUVADA for a PrEP indication
- ☐ Counseled on the importance of scheduled follow-up every 2 to 3 months, including regular HIV-1 screening tests (at least every 3 months), while taking TRUVADA for PrEP to confirm HIV-1 status
- ☐ Discussed the importance of discontinuing TRUVADA for a PrEP indication if seroconversion has occurred, to reduce the development of resistant HIV-1 variants
- ☐ Counseled on the importance of adherence to daily dosing schedule
- ☐ Counseled that TRUVADA for a PrEP indication should be used only as part of a comprehensive prevention strategy
- ☐ Educated on practicing safer sex consistently and using condoms correctly
- ☐ Discussed the importance of the individual knowing their HIV-1 status and, if possible, that of their partner(s)
- ☐ Discussed the importance of and performed screening for sexually transmitted infections (STIs), such as syphilis and gonorrhea, that can facilitate HIV-1 transmission
- ☐ Performed HBV screening test. Offered HBV vaccination as appropriate
- ☐ Confirmed creatinine clearance (CrCl) ≥60 mL/min. If a decrease in CrCl is observed in uninfected individuals while using TRUVADA for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use
- ☐ Confirmed that the uninfected individual at high risk is not taking other HIV-1 medications or hepatitis B medications
- ☐ Provided education on where information about PrEP can be accessed
- ☐ Discussed potential adverse events and side effects
- ☐ Reviewed the TRUVADA Medication Guide with the uninfected individual at high risk
- ☐ Evaluated risk/benefit for women who may be pregnant or may want to become pregnant

Truvada® 200 mg emtricitabine-300 mg tenofovir disoproxil fumarate

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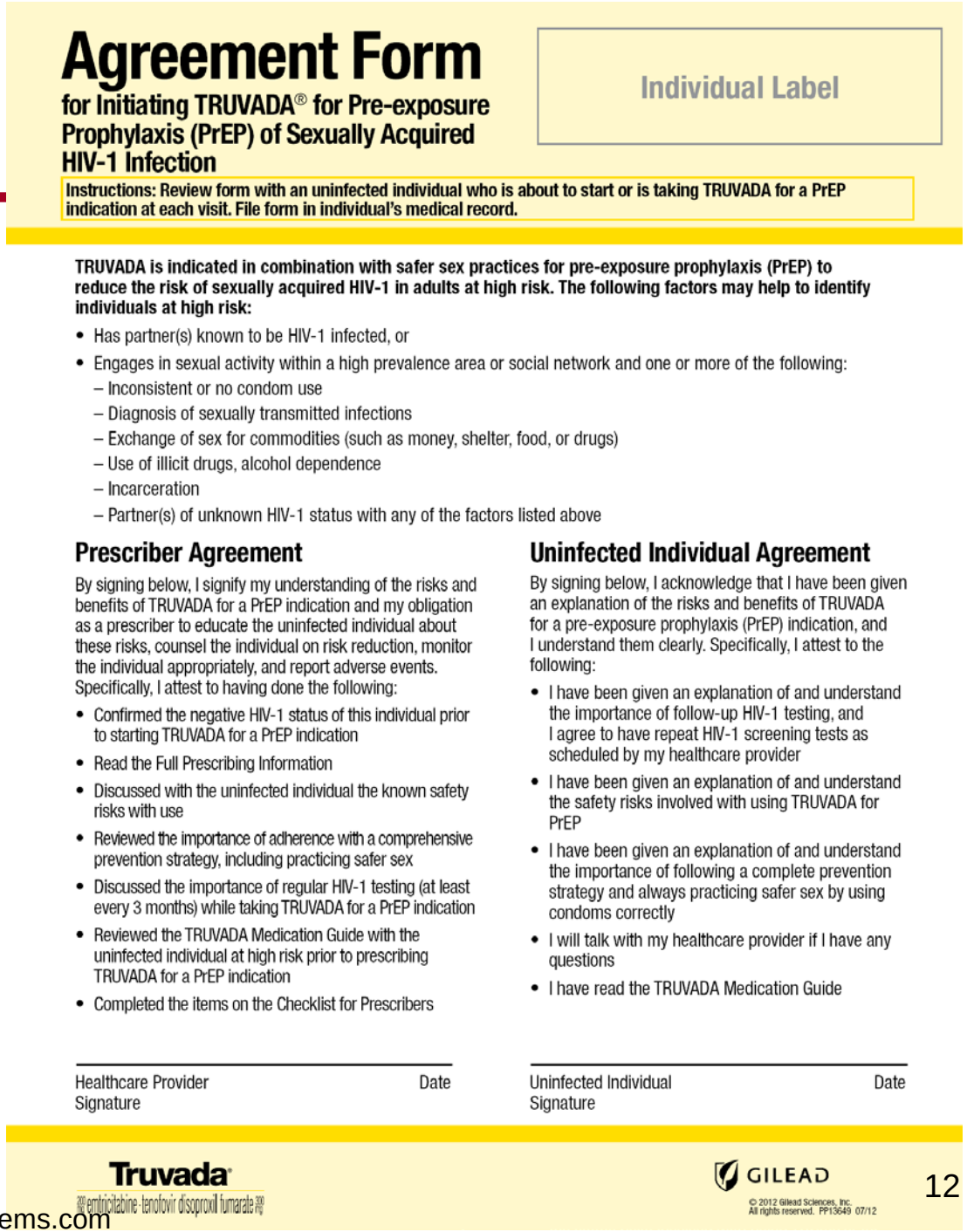
Truvada REMS website. Available at: www.truvadapreprems.com

Agreement Form:

- For prescribers to use with patients to facilitate discussion of appropriate use of PrEP including:
  - Potential safety risks
  - Importance of adherence to a daily regimen
  - Regular assessment of HIV-1 test results
  - Screening for STIs



Agreement Form

for Initiating TRUVADA® for Pre-exposure Prophylaxis (PrEP) of Sexually Acquired HIV-1 Infection

Individual Label

Instructions: Review form with an uninfected individual who is about to start or is taking TRUVADA for a PrEP indication at each visit. File form in individual's medical record.

TRUVADA is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk. The following factors may help to identify individuals at high risk:

- Has partner(s) known to be HIV-1 infected, or
- Engages in sexual activity within a high prevalence area or social network and one or more of the following:
  - Inconsistent or no condom use
  - Diagnosis of sexually transmitted infections
  - Exchange of sex for commodities (such as money, shelter, food, or drugs)
  - Use of illicit drugs, alcohol dependence
  - Incarceration
  - Partner(s) of unknown HIV-1 status with any of the factors listed above

Prescriber Agreement

By signing below, I signify my understanding of the risks and benefits of TRUVADA for a PrEP indication and my obligation as a prescriber to educate the uninfected individual about these risks, counsel the individual on risk reduction, monitor the individual appropriately, and report adverse events. Specifically, I attest to having done the following:

- Confirmed the negative HIV-1 status of this individual prior to starting TRUVADA for a PrEP indication
- Read the Full Prescribing Information
- Discussed with the uninfected individual the known safety risks with use
- Reviewed the importance of adherence with a comprehensive prevention strategy, including practicing safer sex
- Discussed the importance of regular HIV-1 testing (at least every 3 months) while taking TRUVADA for a PrEP indication
- Reviewed the TRUVADA Medication Guide with the uninfected individual at high risk prior to prescribing TRUVADA for a PrEP indication
- Completed the items on the Checklist for Prescribers

Healthcare Provider Signature _____ Date _____

Uninfected Individual Agreement

By signing below, I acknowledge that I have been given an explanation of the risks and benefits of TRUVADA for a pre-exposure prophylaxis (PrEP) indication, and I understand them clearly. Specifically, I attest to the following:

- I have been given an explanation of and understand the importance of follow-up HIV-1 testing, and I agree to have repeat HIV-1 screening tests as scheduled by my healthcare provider
- I have been given an explanation of and understand the safety risks involved with using TRUVADA for PrEP
- I have been given an explanation of and understand the importance of following a complete prevention strategy and always practicing safer sex by using condoms correctly
- I will talk with my healthcare provider if I have any questions
- I have read the TRUVADA Medication Guide

Uninfected Individual Signature _____ Date _____

Truvada® (emtricitabine·tenofovir disoproxil fumarate)

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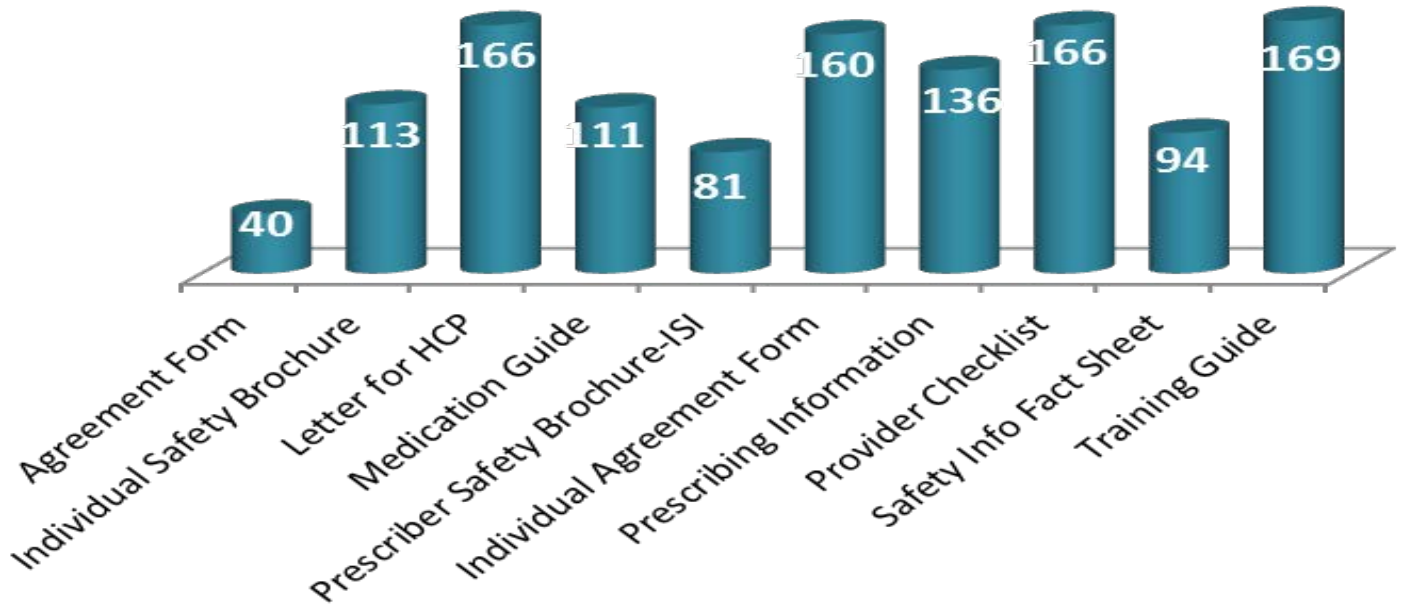
Truvada REMS website. Available at: www.truvadapreprems.com

Utilization of Educational Tools: Downloads



28% of visitors downloaded 1 or more REMS Material

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Data on file, Gilead SciencesAs of 8/2012

Healthcare Provider PrEP Mailings

Mailing Components

- Dear Healthcare Provider Letter
- Training Guide for Healthcare Providers
- Important Safety Information for Healthcare Providers
- Safety Information Fact Sheet
- Agreement Form
- Checklist for Prescribers
- Medication Guide
- Important Safety Information for Uninfected Individuals
- Full Prescribing Information

Recipients

- Healthcare providers that currently treat HIV - MD, DO, NP, PA
- Primary care: IM, FP, GP, PharmD
- OB/GYN
- Infectious Disease
- Addiction Medicine
- Public Health Associations

Educational effort will reach over 200,000 HCPs in the U.S.

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Post-Marketing Measures: Non-REMS

- Post-marketing commitments by Gilead
  - Subsidized HIV-1 viral resistance testing to individuals who seroconvert
  - Post-marketing studies and surveys to further define the safety, efficacy and adherence profiles of Truvada for PrEP along with U.S. prescription data
  - Community Education
    - 1:1 training programs by Gilead Community Medical Scientists on the REMS educational deck
    - Web-based training available on the commercial website
  - Support for independent Continuing Medical Education programs on PrEP

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Truvada Commercial PrEP website Available at: http://start.truvada.com

Additional Non-REMS Resources

- Free HIV & HBV testing for qualified individuals
- Free condoms
- Opt-in reminder service regarding regular testing for HIV and other STDs (to be built)
- Truvada Medication Assistance Program for PrEP for uninfected individuals who lack insurance coverage

Truvada Commercial PrEP website Available at: http://start.truvada.com

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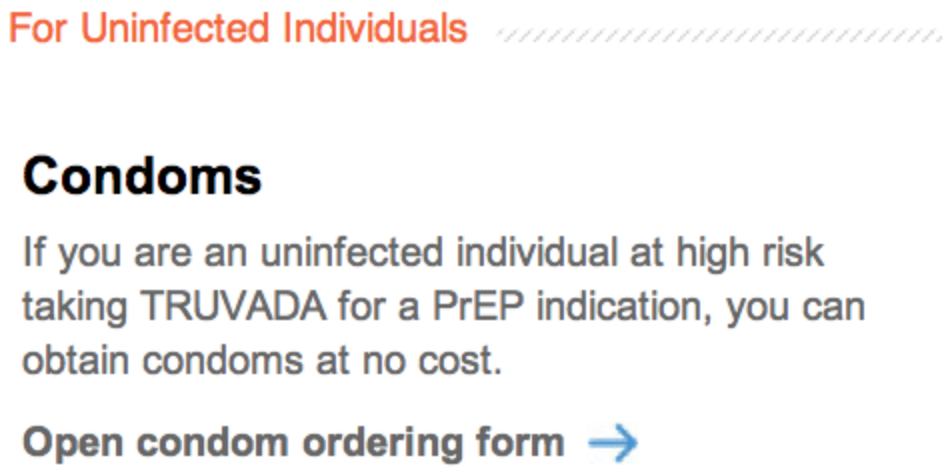
Condoms

- Free condoms are available via hyperlink from
  - www.truvada.com



Truvada Commercial PrEP website Available at: http://start.truvada.com

Medication Assistance Program (MAP) for PrEP:

Program Element	Medication Assistance Program
Eligibility Criteria	US Resident, uninsured or no drug coverage, HIV-negative, low income
Drug Fulfillment	Product dispensed by Covance Specialty Pharmacy, labeled for individual use and shipped to prescriber (30 day supply)
Recertification Period	6 months, 90 day HIV testing status check

Truvada Commercial PrEP website Available at: http://start.truvada.com

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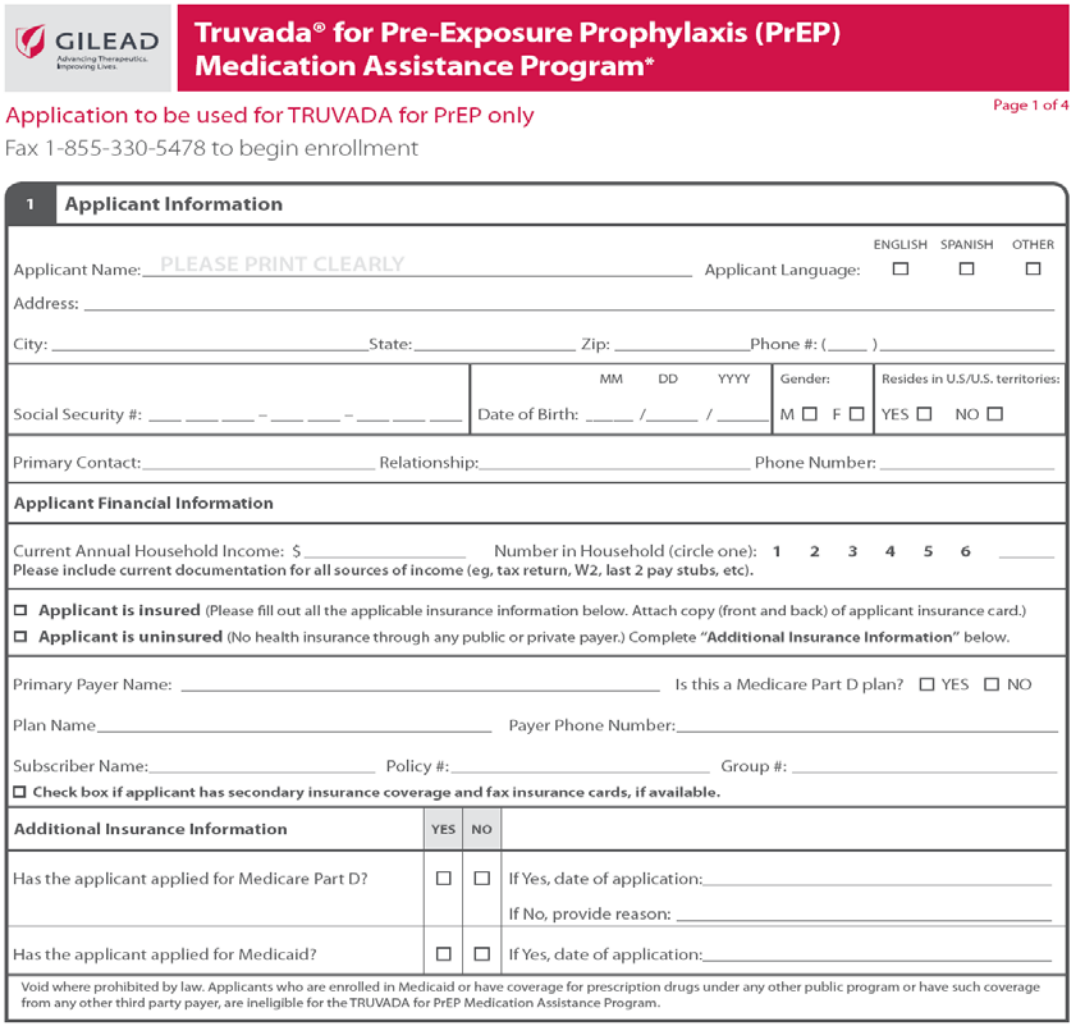
Medication Assistance Form



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Advancing Therapeutics. Improving Lives.

Truvada® for Pre-Exposure Prophylaxis (PrEP)
Medication Assistance Program*

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Application to be used for TRUVADA for PrEP only

Fax 1-855-330-5478 to begin enrollment

1 Applicant Information

Applicant Name: PLEASE PRINT CLEARLY Applicant Language: ENGLISH ☐ SPANISH ☐ OTHER ☐

Address: _____

City: _____ State: _____ Zip: _____ Phone #: (____) _____

Social Security #: ___ ___ ___ – ___ ___ – ___ ___ ___ ___

Date of Birth: MM ____ / DD ____ / YYYY ____

Gender: M ☐ F ☐

Resides in U.S./U.S. territories: YES ☐ NO ☐

Primary Contact: _____ Relationship: _____ Phone Number: _____

Applicant Financial Information

Current Annual Household Income: $_____ Number in Household (circle one): 1 2 3 4 5 6 _____

Please include current documentation for all sources of income (eg, tax return, W2, last 2 pay stubs, etc).

☐ **Applicant is insured** (Please fill out all the applicable insurance information below. Attach copy (front and back) of applicant insurance card.)

☐ **Applicant is uninsured** (No health insurance through any public or private payer.) Complete **"Additional Insurance Information"** below.

Primary Payer Name: _____ Is this a Medicare Part D plan? ☐ YES ☐ NO

Plan Name _____ Payer Phone Number: _____

Subscriber Name: _____ Policy #: _____ Group #: _____

☐ **Check box if applicant has secondary insurance coverage and fax insurance cards, if available.**

Additional Insurance Information	YES	NO	
Has the applicant applied for Medicare Part D?	☐	☐	If Yes, date of application: _____ If No, provide reason: _____
Has the applicant applied for Medicaid?	☐	☐	If Yes, date of application: _____

Void where prohibited by law. Applicants who are enrolled in Medicaid or have coverage for prescription drugs under any other public program or have such coverage from any other third party payer, are ineligible for the TRUVADA for PrEP Medication Assistance Program.

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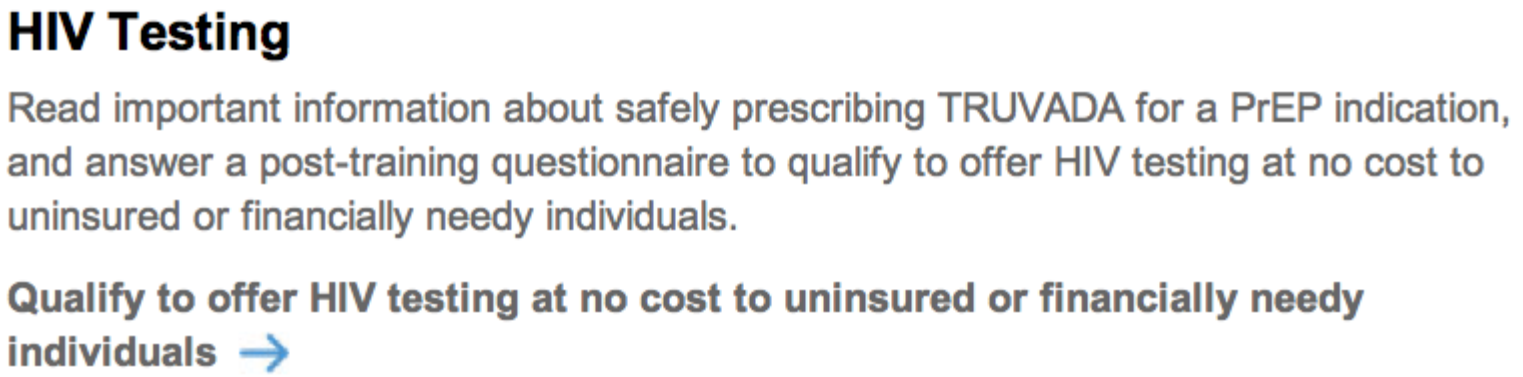
Truvada Commercial PrEP website Available at: http://start.truvada.com

Free HIV/HBV Testing for
Uninsured or Financially Needy Individuals

- Available on Commercial PrEP website.
  - Access also through www.truvada.com via hyperlink
  - Prescribers must first complete an online assessment of the REMS materials, and then may register to offer free testing



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Truvada Commercial PrEP website Available at: http://start.truvada.com

Post-Marketing Measure:
Subsidized Testing in Case of Seroconversion

- Provider contacts Gilead Medical Affairs using phone number displayed on website
  - Provider reports case
  - Medical Affairs contacts LabCorp via email with a copy to the provider
- LabCorp works directly with the Provider – (Gilead not directly involved)
  - LabCorp provides Provider with a one time use specific lab form for resistance testing
  - Provider completes form, gives it to their patient
  - Patient goes to lab to complete test
  - Gilead is directly billed by LabCorp

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Challenges to Implementation of PrEP in the US

- Limited provider experience. Small number of patients enrolled in clinical trials in US (only 3 US sites and < 1000 subjects out of ~10,000 in pivotal studies).
- New strategy with no clear template for administration (many practical questions re implementation) and no PrEP “protocol” in place. Many (most?) LGBT centers in the US do not yet have an active PrEP program in place
- Separation of HIV prevention and treatment services in the US
- Reimbursement for drug and services not clear
- Low level of awareness amongst subjects and providers
- Eligible subjects not clearly defined
- Good news: many of the above issues can be addressed with additional experience/data

Conclusions

- Phase 3b/4 studies are ongoing evaluating TVD,TDF, various dosing strategies, and other ARV combinations for prevention of HIV infection
- Ongoing demonstration projects will yield important information on the use of TVD for PrEP when given in an open label fashion
- A REMS program is in place to ensure the safe and appropriate use of PrEP
  - Educate healthcare providers and uninfected individuals
  - REMS materials are available at www.truvadapreprems.com

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Conclusions

- Gilead is committed to supporting a comprehensive prevention program
  - Provision of educational materials
  - Condoms and assistance programs for medication and testing can be found at www.truvada.com or at http://start.truvada.com
- TVD for PrEP is now being implemented in the US. Initial uptake has been slow but should improve with additional experience in the field and data from ongoing demonstration projects.
  - Similar to a product launch but is a “new strategy” launch
  - Will take 5-10 years to realize the potential of the strategy

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