

## Section 8. Study Drug Responsibilities for Non-Pharmacy Staff

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This section provides instructions to non-pharmacy staff for proper ordering, storage, randomization, dispensing, and record keeping of pharmacist prepared enrollment packets which contain the initial supply of open-label NVP dispensed at enrollment, randomization packets which contain the initial supply of study drug (NVP and NVP placebo) dispensed at randomization and infant packets which contain either open-label NVP or study drug dispensed at follow-up. In addition to these responsibilities, all procedures must be conducted in accordance with the study protocol. The specifications of the protocol take precedence over this document.

### 8.1 Open Label NVP/Study Drug

Throughout this section, the term “open-label NVP” refers to the initial 6 week course of NVP given to all enrolled infants through 6 weeks (42 days) of life and the term “study drug” refers to the product (nevirapine oral suspension 50 mg/5 mL (10 mg/mL) or placebo) provided in the study drug kits to which infants are randomized. Infants may be randomized at any time from 6 weeks (42 days) through 8 weeks (56 days) of life.

#### 8.1.1 HPTN 046 Open-label NVP, Study Drug and Ancillary Supplies

The Pharmacist of Record at each site will be provided with:

- Nevirapine (open-label NVP) 240 mL bottles
- Infant specific study drug kits containing three 240 mL bottles of study drug
- Empty 30 mL bottles (for dispensing of open-label NVP and study drug by the pharmacist for the participant)
- Child resistant closures and non-child resistant closures
- 22 mM and 28 mM Press-in Bottle Adapters (PIBAs)
- Oral syringes (3 mL, 5 mL, and 20 mL oral dispensers)
- Re-sealable plastic bags (3”x4”, 5”x 7”, and 8”x 8”)
- Labels (in English) for the re-sealable plastic bags and 30 mL bottles

### 8.2 Requirements Prior to Shipment to Sites

Before HPTN 046 open-label NVP, study drug and ancillary supplies are sent to the Pharmacist of Record at a Clinical Research Site (CRS), the site must:

- be registered to Version 3.0 of the study protocol by the DAIDS Regulatory Compliance Center (see Section 1.3.5)
- have a Pharmaceutical Affairs Branch (PAB)-approved Pharmacy Establishment Plan
- have PAB-approved SOPs for study drug management and accountability
- have documentation of local drug authority approval for importation of the study drugs (to be submitted to DAIDS PAB and the CORE), and
- have any additional documents required by the country for import of the study drugs (e.g., VAT exemption in South Africa).

The Pharmacist of Record must keep copies of all of the above documents.

It is the responsibility of the Site Investigator and Pharmacist of Record to know the local requirements and to obtain the necessary approvals. The Clinical Research Products Management Center (CRPMC) will notify the consignees each time a shipment has been sent.

Questions regarding shipment of open-label NVP, study drug, and other ancillary supplies to the sites should be directed by the Pharmacist of Record to the HPTN 046 Protocol Pharmacist at DAIDS PAB. Contact information follows.

Scharla G. Estep, R.Ph., M.S.  
Pharmaceutical Affairs Branch, Division of AIDS  
6700-B Rockledge Drive, Room 4111  
Bethesda, MD 20892  
Phone 301-435-3746  
Fax 301-402-1506  
E-mail: [sr72v@nih.gov](mailto:sr72v@nih.gov)

### **8.3 Accountability (Chain of Custody)**

In addition to the requirements of the Pharmacist of Record (*refer to the HPTN 046 Pharmacist Study Drug Management Procedures*), the non-pharmacy study staff must help to assure the chain of custody of open-label NVP and study drug by completing the following documents as directed for each infant participant. Each of these documents will be discussed later in this section.

- HPTN 046 Open-label Nevirapine Prescription
- HPTN 046 Protocol Randomization Record
- Enrollment Packet Request Form (only for sites requesting enrollment packets from the pharmacy prior to enrollment)
- Randomization Packet Request Form (only for sites requesting randomization packets from the pharmacy prior to randomization)
- HPTN 046 Study Drug Prescription
- Dispensing Slips (not required at sites where pharmacists dispense directly to mothers)
- Study Drug Bottle Labels (not required at sites where pharmacists dispense directly to mothers)
- Enrollment Packet Labels (not required at sites where pharmacists dispense directly to mothers)
- Randomization Packet Labels (not required at sites where pharmacists dispense directly to mothers)
- HPTN 046 Record of Receipt of Infant Specific Packets (not required at sites where pharmacists dispense directly to mothers)
- HPTN 046 Record of Return of Infant Specific Packets (not required at sites where pharmacists dispense directly to mothers)
- HPTN 046 Open-Label NVP/Study Drug Request Slip (to be used at follow-up for both open-label NVP requests as well as study drug requests)
- Infant Packet Labels (follow-up only; not required at sites where pharmacists dispense directly to mothers)

### **8.4 Storage of Pharmacist-Prepared Open-Label NVP/Study Drug**

The site pharmacist may prepare enrollment packets, randomization packets and infant packets in advance to be distributed to individual participants at enrollment, randomization and during follow-up visits. These packets must be stored at a controlled temperature (15°C– 30°C) in an area that is always locked and is accessible only to authorized study staff as specified in the pharmacy SOPs/Pharmacy Plan.

Sites may decide to hold packets in the clinic (rather than at the pharmacy) under the conditions described above prior to dispensing to study participants. If sites choose to do this, the temperature of the area where the open-label NVP and/or study drug is stored (e.g., inside the locked cabinet) must be monitored on a continuous basis. If a minimum/maximum thermometer is used rather than a continuous recording device, both temperatures must be recorded each day. (*Note: Sites using a min/max thermometer must have an SOP for the correct use of the thermometer, and appropriate staff must be trained in its use.*) If the temperature falls below 15°C or goes above 30°C, the Pharmacist of Record at the site must be contacted immediately so that s/he can re-dispense the appropriate open-label NVP or study drug as needed. In addition, the Protocol Pharmacist at DAIDS PAB must be notified by email that this occurred, the reason that it occurred, and the mechanisms in place to assure that it will not occur again. This email should come from the Study Coordinator and should copy the Pharmacist of Record at the site.

The open-label NVP and study drug cannot be removed from the clinic until it is dispensed to an individual mother or returned to the pharmacy.

## **8.5 Dispensing of Initial “Enrollment” Supply of Open-label Nevirapine**

*Note: See Section 6.2.1 of the protocol for conditions for exclusion from initial open-label NVP dosing.* The individual who is responsible for actually giving the pharmacist-prepared open-label NVP to the mother can be a study clinician, pharmacist, or another designated individual. However, the following must be completed prior to actual dispensing of open-label NVP to the mother:

**Completion of the HPTN 046 Open-label Nevirapine Prescription.** Dispensing of HPTN 046 open-label NVP to the mother of an infant can occur ONLY after the receipt of a written order of the Investigator of Record (IoR) or upon the order of a licensed clinician listed on the FDA Form 1572 and directly responsible to the IoR as stated on the authorized prescribers list. (*Note: Only clinicians authorized to prescribe in the site’s jurisdiction may write orders for open-label NVP.*) A designated clinic staff member may prepare the prescription in advance by adding the infant’s participant identification (ID) number, completing the Infant’s Date of Birth, and verifying and initialing that informed consent has been provided. All information on the prescription form must be completed prior to the authorized prescriber signing the prescription. A sample HPTN 046 Open-label Nevirapine Prescription is included in Figure 8-1. The authorized prescriber must sign and date the prescription and print his/her name or ID number.

Once the HPTN 046 Open-label Nevirapine Prescription has been completed and signed, sites can dispense the initial HPTN 046 open-label NVP supply in one of three ways: from the clinic using enrollment packets prepared in advance of enrollment, from the clinic using packets prepared after enrollment and from the pharmacy directly. The procedures for each of these methods are described in the sections below. Sites must choose which method they will use prior to study initiation and cannot change methods without consulting the HPTN 046 Protocol Pharmacist.

### **8.5.1 Dispensing of Enrollment Packets to Clinic Staff Prior to Enrollment**

Sites that plan to keep pharmacist-prepared enrollment packets containing the first doses of open-label NVP in the clinic in advance of enrollment must be able to store the packets at 15° - 30°C in a locked, limited access area in the clinic. See Section 8.4 for additional storage requirements. At these sites, designated clinic staff should request enrollment packets from the pharmacy on a weekly basis for women with expected deliveries in the near future using the Enrollment/Randomization Packet Request Form (Figure 8-2). The form should be completed by the designated clinician and should include the name of the clinic for which the enrollment

packets are being requested. All completed Request Forms will be retained in the pharmacy. (Note: The pharmacist should be given at least one working day to prepare enrollment packets.)

Figure 8-1. HPTN 046 Open-Label Nevirapine Prescription

### HPTN 046 OPEN-LABEL NEVIRAPINE PRESCRIPTION

Infant's Participant ID Number: --

Infant's Date of Birth:     
DD MMM YY

Was informed consent provided for infant participation in HPTN 046:  yes  no

Initials of staff member confirming consent documentation: \_\_\_\_\_

Dispense: NVP suspension 50 mg/5ml

- Give 0.6 mL NVP by mouth once daily from 5 days after birth ( $\pm$  2 days) until 2 weeks of age
- 1.5 mL NVP by mouth once daily from 2 to 5 weeks of age
- 1.8 mL NVP by mouth once daily from 5 to 6 weeks (42 days) of age

To be dispensed as:

- One bottle containing 20 mL of Nevirapine suspension 50 mg/5 mL after birth
- Two bottles containing 20 mL each of Nevirapine suspension 50 mg/5 mL for 2 week visit
- Two bottles containing 20 mL each of Nevirapine suspension 50 mg/5 mL for 5 week visit

Authorized Prescriber's Signature: \_\_\_\_\_

Prescriber's Printed Name or ID: \_\_\_\_\_

Date: --  
DD MMM YY

**Figure 8-2. HPTN 046 Enrollment / Randomization Packet Request Form**

**Clinic Name:** \_\_\_\_\_

**Number of Enrollment Packets Requested:** \_\_\_\_\_

**Randomization Packets Requested:**

**Stratum A – Mothers who are receiving antiretroviral therapy (ART) for treatment of HIV**

_____	_____
_____	_____
_____	_____

**Stratum C – Mothers who are NOT receiving antiretroviral therapy (ART) for treatment of HIV**

_____	_____
_____	_____
_____	_____

**Requested by:** *to be signed by person requesting packets* \_\_\_\_\_ **Date:** \_\_\_\_\_

**Prepared by:** *to be signed by pharmacy staff preparing packets* \_\_\_\_\_ **Date:** \_\_\_\_\_

**Dispensed by:** *to be signed by pharmacist* \_\_\_\_\_ **Date:** \_\_\_\_\_

Site Pharmacists, following the directions provided in the *HPTN 046 Pharmacist Study Drug Management Procedures*, will prepare the enrollment packets, which will be used to dispense the initial supply of open-label NVP and oral syringes to the mother. The enrollment packets will include at least 9 oral syringes and not more than 19 oral syringes, a dispensing slip (Dispensing Slip – Enrollment) and one pre-labeled 30 mL bottle containing 20 mL of open-label NVP. The pharmacist will also supply one blank HPTN 046 Open-label Nevirapine Prescription for each enrollment packet prepared if not provided to the clinic in advance. The prescriptions will not be enclosed in the enrollment packet. The enrollment packets will be labeled clearly with the words HPTN 046 Enrollment Packet (Figure 8-3).

**Figure 8-3. Enrollment Packet Label**

<b>HPTN 046 Enrollment Packet</b>	HPTN 046 Enrollment Packet
PID#: _____	PID#: _____
<b>To be dispensed at Enrollment</b>	Dispensed at enrollment on: _____ Date (dd-mmm-yy)
	*Complete label and Attach to clinic dispensing sheet and return to pharmacy*

The HPTN 046 Record of Receipt of Infant-Specific Packets (Figure 8-4) must be used to document dispensing of enrollment packets (containing open-label NVP and oral syringes) to clinic staff. Pharmacy staff will complete the top section (site name, site number, clinic name) and the first five columns on the Record of Receipt. The infant’s participant ID number (PTID) column will be used to document the letters “NVP” to designate the open-label NVP since a PTID number has not yet been assigned to an enrollment packet. When receiving enrollment packets from the pharmacy, clinic staff will verify that “NVP” is indicated in the PTID column, confirm the number of 30 mL bottles (containing 20 mL of open-label NVP), confirm the number and size of the oral syringes, and complete the remaining three columns for each packet. Comments may be recorded in the designated column and on the back of the record if additional space is needed. All Records of Receipt will be retained in the pharmacy.

**Figure 8-4. HPTN 046 Record of Receipt of Infant-Specific Packets**

<b>Site Name:</b>				<b>Clinic Name:</b>				
<b>Site Number:</b>								
<b>PHARMACY STAFF</b>					<b>CLINIC STAFF/RUNNER</b>			<b>COMMENTS</b>
Date Dispensed by Pharmacy dd-MMM-yy	PTID	No. Bottles Dispensed by Pharmacy	No./Size Oral Syringes Dispensed by Pharmacy	RPh Initials	Date Received by Clinic Staff dd-MMM-yy	Time Received by Clinic Staff	Clinic Staff Initials	

The HPTN 046 Record of Return of Infant-Specific Packets (Figure 8-5) must be used to document return of any unused enrollment packets (containing open-label NVP and oral syringes) to the pharmacy staff. Clinic staff will complete the top section (site name, site number, clinic name) and the first five columns on the Record of Return. The PTID column will be used to

document the letters “NVP” to designate the open-label NVP in the packet since a PTID has not yet been assigned to an enrollment packet. When receiving returned enrollment packets from the clinic, pharmacy staff will verify that “NVP” is indicated in the PTID column, confirm the number of 30 mL bottles (containing 20 mL of open-label NVP), confirm the number and size of the oral syringes, and complete the remaining three columns for each packet. Reasons for return (e.g., expiring packet, temperature excursion, etc.) must be recorded in the Comments column and on the back of the record if additional space is needed. All Records of Return will be retained in the clinic.

**Figure 8-5. HPTN 046 Record of Return of Infant-Specific Packets**

<b>Site Name:</b>				<b>Clinic Name:</b>			
<b>Site Number:</b>							

  

CLINIC STAFF /RUNNER					PHARMACY STAFF			Comments
Date Returned by Clinic Staff dd-MMM-yy	PTID	No. Bottles Returned by Clinic Staff	No./Size Oral Syringes Returned by Clinic Staff	Clinic Staff Initials	Date Received by Pharmacy dd-MMM-yy	Time Received by Pharmacy	RPh Initials	

Once the HPTN 046 Open-label Nevirapine Prescription has been completed and signed by an authorized prescriber, the enrollment packet can be removed from the controlled storage area. Enrollment packets will be labeled with a two-part label (Figure 8-3). Each label will include the words HPTN 046 Enrollment Packet and a space for the infant participant ID number. It is the responsibility of the designated enrollment packet dispenser at the clinic to verify that an Enrollment Packet has been removed and to complete the infant participant ID (PID) number on both parts of the enrollment packet label.

The bottle of open-label NVP inside the enrollment packet will be labeled with a three-part label (Figure 8-6). It is the responsibility of the enrollment packet dispenser to fill in the infant participant ID (PID) number in all three areas in which it is required.

**Figure 8-6. Open-Label NVP Bottle Label**

PID#: _____ Nevirapine 10mg/mL Suspension      20 ml Date Dispensed: _____ Expires: _____ Give _____ ml by mouth every day. Shake gently before using Store at 15° - 30°C <small>Caution: New Drug. Limited by United States law to investigational use</small>	DETACH HERE BEFORE DISPENSING TO PARTICIPANT	PID#: _____ Lot #: _____
	DETACH HERE BEFORE DISPENSING TO PARTICIPANT	PID#: _____ Lot #: _____

It is the responsibility of the individual dispensing the open-label NVP to the mother of the infant (dispenser) to ensure that the pharmacist has completed all of the information on each part of the enrollment packet and open-label NVP bottle labels and that the designated clinician has completed the infant participant ID number. It is also the dispenser’s responsibility to verify that the dose to be administered from day 3 to 7 after the birth date to 2 weeks of age is accurate and that the syringes are marked correctly prior to dispensing the packet (syringes and bottle) to the mother. Once an enrollment packet has been designated and prior to giving the infant’s

enrollment packet containing the open-label NVP to the mother, the dispenser will remove the 30 mL bottle of open-label NVP and tear off the completed removable portions of the labels (Figure 8-6). One of the two removable study drug bottle labels will be placed on study source records and the other will be adhered to the back of the HPTN 046 Dispensing Slip - Enrollment. The dispenser will complete HPTN 046 Dispensing Slip - Enrollment (Figure 8-7) included in the enrollment packet by adding the infant participant ID (PID) number, date of dispensing, and his/her initials. The dispenser will add the dispensing date to the Enrollment packet label (Figure 8-3) and attach the completed right portion of the label to the HPTN 046 Dispensing Slip in the area indicated.

**Figure 8-7. HPTN 046 Dispensing Slip - Enrollment**

<p>Attach label from outside of Infant's Enrollment Packet here</p>	<p>Dispensed to Infant PID #: _____</p> <p>On: _____ By: _____</p>
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The mother will receive the HPTN 046 open-label NVP and oral syringes in a re-sealable plastic bag prior to discharge with instructions to begin administration of the open-label NVP to the infant 3 to 7 days after birth. Administration instructions to be given to mothers are included in Section 8.8.

If the mother does not begin dosing the infant when instructed, she should start the infant's regimen as soon as possible thereafter. *Note: See Section 6.2.1 of the protocol for additional information.*

Dispensing slips and the top copy of completed HPTN 046 Open-label Nevirapine prescriptions should be returned to the pharmacy by the end of the day on which dispensing occurred. Documents must be returned within 5 working days of dispensing. A pharmacist will not be able to dispense any additional open-label NVP for an infant participant if the prescription and dispensing slip have not been completed appropriately and sent to the pharmacy. The dispensing slip and original prescription must be kept in the pharmacy. The bottom copy of the prescription will be filed in the participant research record.

### **8.5.2 Dispensing Open-Label NVP by Pharmacists to Clinic Staff after Enrollment**

Sites that choose to have their pharmacist dispense open-label NVP and syringes to the clinic staff for distribution to the infant participant after enrollment must first complete the Open-label Nevirapine Prescription as instructed in Section 8.5. Unsigned HPTN 046 Open-label Nevirapine Prescriptions may be obtained from the pharmacist as needed for each of the clinics where enrollment will occur. Once the prescription has been completed, clinic staff will bring the top copy of the completed prescription to the site pharmacy.

Upon receipt of a completed, signed HPTN 046 Open-label Nevirapine Prescription, the site pharmacist, following the directions provided in the *HPTN 046 Pharmacist Study Drug Management Procedures*, will prepare the infant-specific packet that will be used to dispense the initial supply of open-label NVP and oral syringes to the mother. The packet will include at least 9 and not more than 19 oral syringes, a dispensing slip (Dispensing Slip – Enrollment) and one

pre-labeled 30 mL bottle containing 20 mL of study drug. The packet will be labeled clearly with the infant participant ID (PID) number.

The HPTN 046 Record of Receipt of Infant Specific Packets (Figure 8-4) must be used to document dispensing of infant-specific packets (containing open-label NVP and oral syringes) to clinic staff. Pharmacy staff will complete the top section (site name, site number, clinic name) and the first five columns on the Record of Receipt. When receiving infant specific packets from the pharmacy, clinic staff will verify the infant participant ID number (PID), confirm the number of 30 mL bottles (containing 20 mL of open-label NVP), confirm the number and size of the oral syringes, and complete the remaining three columns for each PTID. Comments may be recorded in the designated column and on the back of the record if additional space is needed. All Records of Receipt will be retained in the pharmacy.

It is the responsibility of the individual dispensing the open-label NVP to the participant (dispenser) to ensure that the pharmacist has completed all of the information on each part of the enrollment packet label and the open-label NVP bottle label. It is also the dispenser's responsibility to verify that the dose to be administered from from day 3 to 7 after the birth date to 2 weeks of age is accurate and that the syringes are marked correctly prior to dispensing the packet (syringes and bottle) to the mother. Immediately before giving the open-label NVP to the mother, the dispenser will obtain the 30 mL bottle of open-label NVP and tear off the completed removable portions of the labels (Figure 8-6). One label will be placed on study source records and the other will be adhered to the back of the HPTN 046 Dispensing Slip - Enrollment (Fig 8-7). The dispenser will complete HPTN 046 Dispensing Slip - Enrollment included in the enrollment packet by adding the infant participant ID number, date of dispensing, and his/her initials. The dispenser will add the dispensing date to the packet label and attach the completed right portion of the label to the HPTN 046 Dispensing Slip in the area indicated.

The mother will receive the HPTN 046 open-label NVP and oral syringes in a re-sealable plastic bag prior to discharge with instructions to begin administration of the study drug to the infant from day 3 to 7 after the birth date. Administration instructions to be given to mothers are included in Section 8.8.

If the mother does not begin dosing the infant when instructed, she should start the infant's regimen as soon as possible thereafter. *Note: See Section 6.2.1 of the protocol for additional information.*

Completed dispensing slips should be returned to the pharmacy by the end of the day on which dispensing occurred. Slips must be returned within 5 working days of dispensing. A pharmacist will not be able to dispense any additional open-label NVP for an infant participant if the dispensing slip has not been completed appropriately and sent to the pharmacy. The dispensing slip and original prescription must be kept in the pharmacy.

The HPTN 046 Record of Return of Infant Specific Packets (Figure 8-5) must be used to document return of infant-specific packets (containing open-label NVP and oral syringes) to pharmacy staff when necessary. Clinic staff will complete the top section (site name, site number, clinic name) and the first five columns on the Record of Receipt. When receiving infant specific packets back from the clinic, pharmacy staff will verify the infant's participant ID number (PTID), confirm the number of 30 mL bottles (containing 20 mL of open-label NVP), confirm the number and size of the oral syringes, and complete the remaining three columns for

each PTID. Reasons for return (e.g., mother left the clinic prior to receiving packet) must be recorded in the Comments column and on the back of the record if additional space is needed. All Records of Return will be retained in the clinic.

### **8.5.3 Dispensing Open-Label NVP by Pharmacist Directly to Mothers**

Sites that choose to have the pharmacist dispense open-label NVP and syringes directly to the mother after enrollment must first complete the Open-label Nevirapine Prescription as instructed in Section 8.5. Unsigned HPTN 046 Open-label Nevirapine Prescriptions may be obtained from the pharmacist as needed for each of the clinics where enrollment will occur. Designated site staff will give the top copy of the completed prescription to the mother, who will carry it to the pharmacy.

Upon receipt of a completed, signed HPTN 046 Open-label Nevirapine Prescription from the infant participant's mother, the site pharmacist, following the directions provided in the *HPTN 046 Pharmacist Study Drug Management Procedures* will prepare the infant-specific packet that will be used to dispense the initial supply of open-label NVP and oral syringes to the mother. The packet will include at least 9 and not more than 19 oral syringes and one pre-labeled 30 mL bottle containing 20 mL of open-label NVP. The pharmacist will complete all information on the Enrollment Packet Label (Figure 8-3) and Open-Label NVP Bottle Label (Figure 8-6). S/he will attach the left side of the packet label to the re-sealable plastic bag and the right side will be detached at the time the packet is given to the mother and attached to an infant specific dispensing log which will be kept in the pharmacy (refer to *HPTN 046 Pharmacist Study Drug Management Procedures*). The Open-Label NVP Bottle Labels will be set aside to be placed on the infant's source documents. An SOP must be in place to describe the process that will be followed.

The mother will receive the HPTN 046 open-label NVP and oral syringes in a re-sealable plastic bag with instructions to begin administration of the open-label NVP to the infant from day 3 to 7 after the birth date. Administration instructions to be given to mothers are included in Section 8.8.

If the mother does not begin dosing to the infant when instructed, she should start the infant's regimen as soon as possible thereafter. *Note: See Section 6.2.1 of the protocol for additional information.*

### **8.5.4 Dispensing Open-Label NVP for Multiple Births after Enrollment**

In the case of a multiple birth, a separate Open-label Nevirapine Prescription must be completed for each infant. The word "multiple birth" must be written below each Infant's Participant ID Number on the prescription. An enrollment packet should be dispensed for each infant as directed in the appropriate section above (e.g. for twins – two enrollment packets would be dispensed).

## 8.6 Dispensing of Initial “Randomized” Supply of Study Drug

*Note: See Section 6.2.3 of the protocol for conditions for exclusion from initial study drug dosing in randomized infants.*

The individual who is responsible for actually giving the pharmacist-prepared study drug to the mother can be a study clinician, pharmacist, or another designated individual. However, the following two steps must be completed prior to actual dispensing of study drug to the mother:

**Step 1: Completion of the HPTN 046 Study Drug Prescription** Randomization of an infant to HPTN 046 study drug can occur ONLY upon the receipt of a written order of the Investigator of Record (IoR) or upon the order of a licensed clinician listed on the FDA Form 1572 and directly responsible to the IoR as stated on the authorized prescribers list. (*Note: Only clinicians authorized to prescribe in the site’s jurisdiction may write orders for study drugs.*) A designated clinic staff member may prepare the prescription in advance by adding the infant’s participant ID number, verifying and initialing that informed consent has been provided, identifying the appropriate stratum and documenting the visit week or month (e.g. 6 week visit). All information on the HPTN 046 Study Drug Prescription must be completed with the exception of the kit number, which will be obtained after the prescription is signed and added to the prescription by the person designated to assign kits. A sample HPTN 046 Study Drug Prescription is included in Figure 8-8. The authorized prescriber must sign and date the prescription and print his/her name or ID number.

Figure 8-8. HPTN 046 Study Drug Prescription

### HPTN 046 STUDY DRUG PRESCRIPTION

Infant's Participant ID Number: --

Infant's Date of Birth:     
DD MMM YY

Was informed consent provided for infant participation in HPTN 046:  yes  no  
Initials of staff member confirming consent documentation: \_\_\_\_\_

Stratum:  A – Mothers who are receiving antiretroviral therapy (ART) for treatment of HIV  
 C – Mothers who are NOT receiving antiretroviral therapy (ART) for treatment of HIV

Kit ID Number  Initials of kit assigner: \_\_\_\_\_ Date: \_\_\_\_\_

Dispense: NVP suspension 50 mg/5mL - or - Placebo suspension

- Give 2 mL by mouth once daily from 6 ( $\geq$  43 days) to 8 weeks of age
- 2.2 mL by mouth once daily from 8 weeks to 3 months of age
- 2.4 mL by mouth once daily from 3 to 4 months of age
- 2.6 mL by mouth once daily from 4 to 5 months of age
- 2.8 mL by mouth once daily from 5 to 6 months of age

To be dispensed as:

- Two bottles containing 20 mL each of study product for 6 week visit
- Five bottles containing 20 mL each of study product for 8 week visit
- Five bottles containing 20 mL each of study product for 3 month visit
- Six bottles containing 20 mL each of study product for 4 month visit
- Six bottles containing 20 mL each of study product for 5 month visit

Authorized Prescriber's Signature: \_\_\_\_\_

Prescriber's Printed Name or ID: \_\_\_\_\_

Date: --  
DD MMM YY Visit:  week **OR**  month

**Step 2: Assignment of the kit number.** After the infant’s eligibility has been determined, the investigator or designee has documented the review of the eligibility requirements in the study source documents, and a completed HPTN 046 prescription has been signed (as instructed above), a designated staff member (referred to as the kit assigner) can assign the next infant study drug kit to the infant participant.

Each infant study drug kit is identified by a pre-printed 5-digit (XXXXX) number. The first digit identifies the site, and the remaining digits are unique sequential kit numbers within each site.

There are two randomization strata for this study:

- A – Mothers who are receiving antiretroviral therapy (ART) for treatment of HIV
- C – Mothers who are NOT receiving antiretroviral therapy (ART) for treatment of HIV

The Clinic Coordinator will initially receive two HPTN 046 Protocol Randomization Records (one for each stratum) from the SDMC for each of the clinics where randomization will occur. A separate log will be maintained for each stratum for each clinic. Assigning a kit number is done by selecting the next sequential infant kit number from the Protocol Randomization Log for the appropriate stratum, A or C. Each site/clinic should designate one or two people to assign kit numbers and maintain the Protocol Randomization Records. The effective point of randomization for this study is the assignment of a kit to an infant participant, which thereby randomizes the infant.

The example below (Figure 8- 9) is the top section of the HPTN 046 Protocol Randomization Record for Stratum C - Mothers who are NOT receiving antiretroviral therapy (ART) for treatment of HIV.

**Figure 8-9. Sample HPTN 046 Protocol Randomization Record**

<b>Site Name:</b>		<b>Investigator:</b>		
<b>Clinic Name:</b>		<b>Investigator #:</b>		
	<b>Site Number:</b>			
<b>Stratum C: Mothers who are NOT receiving antiretroviral therapy (ART) for <u>treatment</u> of HIV</b>				
Infant Kit #	Assigned to Participant ID # (Infant)	Date Assigned	Clinic Staff Initials	Comments
XXXXX				
XXXXX				
XXXXX				

The kits must be assigned in sequential order from the appropriate Protocol Randomization Record. Upon assignment of a kit number to an infant, the assigner should record the infant’s participant ID number, the date assigned, their initials and any comments (if needed) next to the corresponding infant kit number on the appropriate Randomization Record and complete the Prescription by adding the kit number, their initials, and the date assigned.

Once the HPTN 046 Study Drug Prescription has been completed and the infant kit number has been assigned, sites can dispense the initial study drug supply in one of three ways: from the clinic using randomization packets prepared in advance of randomization, from the clinic using packets prepared after randomization and from the pharmacy directly. The procedures for each of these methods are described in the sections below. Sites must choose which method they will use prior to study initiation and cannot change methods without consulting the HPTN 046 Protocol Pharmacist.

*Note: Once a study drug kit is assigned to a participant, it can **never** be re-assigned to anyone else, even if study drug dosing is never initiated.*

*Note: For procedures to be followed for multiple births, see section 8.6.4 below.*

### **8.6.1 Dispensing of Randomization Packets to Clinic Staff Prior to Randomization**

Sites that plan to keep pharmacist-prepared randomization packets containing the first doses of study drug in the clinic in advance of randomization must be able to store the packets at 15° - 30°C in a locked, limited access area in the clinic. See Section 8.4 for additional storage requirements. At these sites, designated clinic staff should request randomization packets from the pharmacy on a weekly basis for infants who may be eligible for randomization in the near future using the Enrollment / Randomization Packet Request Form (Figure 8-2). The form should be completed by the designated kit assigner or designee and should include the name of the clinic for which the randomization packets are being requested as well as the next sequential kit numbers for the appropriate strata. All completed Request Forms will be retained in the pharmacy. A system must be in place so that duplicate randomization packets are not requested from the pharmacist. The pharmacist should be given at least one working day to prepare randomization packets.

Site Pharmacists, following the directions provided in the *HPTN 046 Pharmacist Study Drug Management Procedures*, will prepare the randomization packets, which will be used to dispense the initial supply of study drug and oral syringes to the mother. The randomization packets will include the appropriate quantity of oral syringes, a dispensing slip (Dispensing Slip – Randomization Fig 8-12) and two pre-labeled 30 mL bottle containing 20 mL of study drug. The pharmacist will also supply one blank HPTN 046 Study Drug Prescription for each randomization packet prepared if not provided to the clinic in advance. The prescriptions will not be enclosed in the randomization packet. The randomization packets will be labeled clearly with the kit ID number and stratum.

The HPTN 046 Record of Receipt of Infant-Specific Packets (Figure 8-4) must be used to document dispensing of randomization packets (containing study drug and oral syringes) to clinic staff. Pharmacy staff will complete the top section (site name, site number, clinic name) and the first five columns on the Record of Receipt. The PTID column will be used to document the infant kit number since a PTID number has not yet been assigned to a specific kit. When receiving randomization packets from the pharmacy, clinic staff will verify the infant kit number, confirm the number of 30 mL bottles (containing 20 mL of study drug), confirm the number and size of the oral syringes, and complete the remaining three columns for each kit number. Comments may be recorded in the designated column and on the back of the record if additional space is needed. All Records of Receipt will be retained in the pharmacy.

The HPTN 046 Record of Return of Infant-Specific Packets (Figure 8-5) must be used to document return of any unused randomization packets (containing study drug and oral syringes) to the pharmacy staff. Clinic staff will complete the top section (site name, site number, clinic

name) and the first five columns on the Record of Return. The PTID column will be used to designate the infant kit number on the randomization packet. When receiving returned randomization packets from the clinic, pharmacy staff will verify the infant kit number on the randomization packet, confirm the number of 30 mL bottles (containing 20 mL of study drug), confirm the number and size of the oral syringes, and complete the remaining three columns for each kit number. Reasons for return (e.g., expiring packet, temperature excursion, etc.) must be recorded in the Comments column and on the back of the record if additional space is needed. All Records of Return will be retained in the clinic.

Once the HPTN 046 Study Drug Prescription has been signed and the Kit ID Number has been assigned to an infant (i.e., the baby has been randomized), the randomization packet can be removed from the controlled storage area. Randomization packets will be labeled with a two-part label. Each label will include the kit number and a space for the infant’s participant ID number (PID) (Figure 8-10). It is the responsibility of the designated kit assigner at the clinic to verify the appropriate Kit ID Number has been removed and to complete the infant’s participant ID number (PID) on both parts of the randomization packet label.

**Figure 8-10. Randomization Packet Label**

<p><b>HPTN 046 Randomization Packet</b></p> <p>PID#: _____</p> <p>Kit ID#: _____ XXXXX</p> <p><b>To be dispensed at Randomization</b></p>	<p>HPTN 046 Randomization Packet</p> <p>PID#: _____</p> <p>Kit ID#: _____ XXXXX</p> <p>Dispensed at randomization on:</p> <p>_____</p> <p>Date (dd-mmm-yy)</p> <p><i>*Complete label and Attach to clinic dispensing sheet and return to pharmacy*</i></p>
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The bottle of study drug inside the randomization packet will be labeled with a three-part label (Figure 8-11). It is the responsibility of the kit assigner to fill in the infant’s participant ID number in all three areas in which it is required.

**Figure 8-11. Study Drug Bottle Label**

<p>PID#: _____</p> <p><b>HPTN 046 Study Drug</b>          20 ml per bottle Expires: <u>xx/xx</u>  <b>Store at 15°– 30°C (59°F – 86°F)</b>          Shake gently before using          Give <u>0.6</u> ml by mouth every day.  <i>Caution: New Drug. Limited by Federal (USA) law to Investigational use</i></p>	<p>DETACH HERE BEFORE DISPENSING</p>	<p>PID#: _____</p> <p>Kit ID#: _____ XXXXX</p> <p>Bottle ID#: _____ X</p>	<p>DETACH HERE BEFORE DISPENSING</p>	<p>PID#: _____</p> <p>Kit ID#: _____ XXXXX</p> <p>Bottle ID#: _____ X</p>
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It is the responsibility of the individual dispensing the study drug to the participant (dispenser) to ensure that the pharmacist has completed all of the information on each part of the randomization packet and study drug bottle labels and that the designated kit assigner has completed the infants’s participant ID number (PID). It is also the dispenser’s responsibility to verify that the dose to be administered for the infant’s age is accurate and that the syringes are marked correctly prior to dispensing the packet (syringes and bottle) to the mother.

It is critical to remember that if an infant is randomized at a visit later than the 6 week visit (e.g. the infant is 8 weeks of age when randomized), it is the responsibility of the individual dispensing the study drug to contact the Pharmacist to obtain the additional 30 mL bottles containing 20 mL of study drug that will be needed. It will be necessary for the Pharmacist to receive the signed HPTN 046 Study Drug Prescription prior to dispensing the additional bottles to the clinic staff.

Once an infant study drug kit has been assigned and prior to giving the randomization packet containing the study drug to the mother, the dispenser will remove the two 30 mL bottles of study drug and tear off the completed removable portions of the labels (Figure 8-11). For each bottle, one of the two removable study drug bottle labels will be placed on study source records and the other will be adhered to the Infant's Study Drug Dosing (IDD) DataFax Form. The dispenser will complete HPTN 046 Dispensing Slip - Randomization (Figure 8-12) included in the randomization packet by adding the infant participant ID number, date of dispensing, and his/her initials. The dispenser will add the dispensing date to the Randomization Packet Label (Figure 8-10) and attach the completed right portion of the label to the HPTN 046 Dispensing Slip in the area indicated.

**Figure 8-12. HPTN 046 Dispensing Slip - Randomization**

Attach label from outside of Infant's Randomization Packet here	Dispensed to Infant PID #: _____ On: _____ By: _____
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Dispensing slips and the top copy of completed HPTN 046 Study Drug prescriptions should be returned to the pharmacy by the end of the day on which dispensing occurred. Documents must be returned within 5 working days of dispensing. A pharmacist will not be able to dispense any additional study drug for an infant participant if the prescription and dispensing slip has not been completed appropriately and sent to the pharmacy. The dispensing slip and original prescription must be kept in the pharmacy. The bottom copy of the prescription will be filed in the participant research record.

**8.6.2 Dispensing of Study Drug by Pharmacists to Clinic Staff after Randomization**

Sites that choose to have their pharmacist dispense study drug and syringes to the clinic staff for distribution to the infant participant after randomization must complete steps 1 and 2 in Section 8.6. Unsigned HPTN 046 Study Drug Prescriptions may be obtained from the pharmacist as needed for each of the clinics where randomization will occur. Once the prescription has been completed and the kit number has been assigned, clinic staff will bring the top copy of the completed prescription to the site pharmacy.

Upon receipt of a completed, signed HPTN 046 Study Drug Prescription Form, the site pharmacist, following the directions provided in the *HPTN 046 Pharmacist Study Drug Management Procedures*, will prepare the infant-specific packet that will be used to dispense the initial supply of study drug and oral syringes to the mother. The randomization packets will include the appropriate quantity of oral syringes, a dispensing slip (Dispensing Slip - Randomization) and the appropriate number of pre-labeled 30 mL bottles containing 20 mL of

study drug. (The number of bottles will be determined by the visit week or month documented on the prescription.) The packet will be labeled clearly with the participant ID number, the kit ID number and the stratum.

The HPTN 046 Record of Receipt of Infant Specific Packets (Figure 8-4) must be used to document dispensing of infant-specific packets (containing study drug and oral syringes) to clinic staff. Pharmacy staff will complete the top section (site name, site number, clinic name) and the first five columns on the Record of Receipt. When receiving infant specific packets from the pharmacy, clinic staff will verify the infant's participant ID number, confirm the number of 30 mL bottles (containing 20 mL of study drug), confirm the number and size of the oral syringes, and complete the remaining three columns for each PTID. Comments may be recorded in the designated column and on the back of the record if additional space is needed. All Records of Receipt will be retained in the pharmacy.

It is the responsibility of the individual dispensing the study drug to the participant (dispenser) to ensure that the pharmacist has completed all of the information on each part of the randomization packet label and the study drug bottle label. It is also the dispenser's responsibility to verify the appropriate number of bottles are being dispensed, the dose to be administered for the infant's age is accurate and that the syringes are marked correctly prior to dispensing the packet (syringes and bottle) to the mother. Immediately before giving the study drug to the mother, the dispenser will obtain each of the 30 mL bottles of study drug and tear off the completed removable portions of the labels (Figure 8-11). One label will be placed on study source records and one label will be adhered to the Infant's Study Drug Dosing (IDD) DataFax form. The dispenser will complete HPTN 046 Dispensing Slip - Randomization (Figure 8-12) included in the randomization packet by adding the infant participant ID number, date of dispensing, and his/her initials. The dispenser will add the dispensing date to the packet label (Figure 8-10: Randomization Packet Label) and attach the completed right portion of the label to the HPTN 046 Dispensing Slip in the area indicated.

Completed dispensing slips should be returned to the pharmacy by the end of the day on which dispensing occurred. Slips must be returned within 5 working days of dispensing. A pharmacist will not be able to dispense any additional study drug for an infant participant if the dispensing slip has not been completed appropriately and sent to the pharmacy. The dispensing slip and original prescription must be kept in the pharmacy.

The HPTN 046 Record of Return of Infant Specific Packets (Figure 8-5) must be used to document return of infant-specific packets (containing study drug and oral syringes) to pharmacy staff when necessary. Clinic staff will complete the top section (site name, site number, clinic name) and the first five columns on the Record of Receipt. When receiving infant specific packets back from the clinic, pharmacy staff will verify the PTID, confirm the number of 30 mL bottles (containing 20 mL of study drug), confirm the number and size of the oral syringes, and complete the remaining three columns for each PTID. Reasons for return (e.g., mother left the clinic prior to receiving packet) must be recorded in the Comments column and on the back of the record if additional space is needed. All Records of Return will be retained in the clinic.

### **8.6.3 Dispensing of Study Drug by Pharmacist Directly to Mothers**

Sites that choose to have the pharmacist dispense study drug and syringes directly to the mother after randomization must complete steps 1 and 2 in Section 8.6. Unsigned HPTN 046 Study Drug Prescriptions may be obtained from the pharmacist as needed for each of the clinics where

randomization will occur. Designated site staff will give the top copy of the completed prescription to the mother, who will carry it to the pharmacy.

Upon receipt of a completed, signed HPTN 046 Study Drug Prescription from the infant participant's mother, the site pharmacist, following the directions provided in the *HPTN 046 Pharmacist Study Drug Management Procedures* will prepare the infant-specific packet that will be used to dispense the initial supply of study drug and oral syringes to the mother. The randomization packets will include the appropriate quantity of oral syringes, a dispensing slip (Dispensing Slip - Randomization) and the appropriate number of pre-labeled 30 mL bottles containing 20 mL of study drug (based on the visit week or month documented on the prescription). The pharmacist will complete all information on the packet label (Figure 8-10) and study drug bottle label (Figure 8-11). S/he will attach the left side of the packet label to the re-sealable plastic bag and the right side will be detached at the time the packet is given to the mother and attached to an infant specific dispensing log which will be kept in the pharmacy (refer to *HPTN 046 Pharmacist Study Drug Management Procedures*). The study drug bottle labels will be set aside to be placed on the infant's source documents and Infant's Study Drug Dosing (IDD) DataFax form. An SOP must be in place to describe the process that will be followed.

#### **8.6.4 Dispensing Study Drug for Multiple Births after Randomization**

In the case of a multiple birth, study drug will initially be dispensed to all infants from one infant study drug kit. Please note however, that a randomization packet with the appropriate number of pre-labeled 30 mL bottles containing 20 mL of study drug and the appropriate quantity of syringes must be prepared for each infant as directed in the sections above. The participant ID number of the first born infant should be recorded on the HPTN 046 Protocol Randomization Record with a note in the comments field indicating a multiple birth. A separate Study Drug Prescription must be completed for each infant. The identical infant kit number must be recorded on each infant's HPTN 046 Study Drug Prescription at this time and the word "multiple birth" written below each Infant's Participant ID Number.

For sites whose procedures dictate the dispensing of randomization packets to clinic staff prior to randomization, the site staff should record the participant ID number of the first born infant on the enclosed study drug bottle labels and the packet labels and dispensing slips. Two prescriptions must be provided to the Pharmacist in order to receive the additional randomization packet needed for the multiple birth. All labels for the second born infant (and any other multiple births) will be completed by the Pharmacist at the time of preparation of the subsequent randomization packet.

The corresponding bottle labels should be placed on each infant's source documents and each Infant's Study Drug Dosing (IDD) DataFax form.

Prior to the next visit, the pharmacist will contact the SDMC as instructed in the *HPTN 046 Pharmacist Study Drug Management Procedures* to inform them of the multiple birth and the need for additional study drug kit(s). The SDMC will send an email to the Pharmacist of Record and Clinic Coordinator assigning an additional kit number to replace the initial assignment for each additional multiple birth. A copy of this email should be attached to the appropriate prescription in the infant's research record (by the Clinic Coordinator) and in the pharmacy (by the Pharmacist of Record). The email should be initialed and dated by the person attaching it to the prescription. Study drug will be dispensed from the appropriate kit number for each individual infant at the next scheduled visit.

## 8.7 Follow-up Visit Dispensing Procedures for Open-Label NVP and Study Drug

At each scheduled follow-up visit, designated clinicians should confirm and record in source documents that the participant is eligible for continued dosing according to the protocol prior to dispensing additional open-label NVP or study drug. *Note: See Sections 6.2.2 and 6.2.3 of the protocol for reasons subsequent doses of open-label NVP or study drug may be temporarily held or permanently discontinued.* The site IoR is responsible for ensuring that these protocol specifications are followed for all participants. Infants will only be eligible for dose escalation/adjustment if they are within the visit window for the appropriate scheduled visit.

### 8.7.1 Open-Label NVP/Study Drug Request Slips

#### Scheduled Visits

Clinic staff should use the HPTN 046 Open-label NVP/Study Drug Request Slip (Figure 8-13) to communicate to pharmacy staff that a participant is expected for a follow-up visit during the dosing period of an infant's participation. The slip should also be used to communicate clinic staff decisions to hold open-label NVP/study drug for a participant or to resume open-label NVP/study drug use after a prior hold. The Open-Label NVP/Study Drug Request Slip is a two-part no carbon required (NCR) document that is available in pads of 50 from the DAIDS Clinical Research Product Management Center. The Pharmacist of Record will order bulk supplies of the pads for use by clinic staff throughout the course of the study. The Open-label NVP/Study Drug Request Slip should be completed as follows:

- Record the clinic name at the top of the slip. The name recorded must be identical to the clinic name listed on the protocol randomization log, unless an alternative clinic name or abbreviation is designated in the SOP for open-label NVP/study drug re-supply during follow-up.
- Record the PTID, the Kit Identification Number assigned to the participant (for infants that are randomized), and the infant date of birth in the boxes provided.
- Mark the appropriate box for RE-SUPPLY, HOLD, or RESUME to indicate the action to be taken in the study pharmacy. When marking RE-SUPPLY or RESUME, record the number of bottles of open-label NVP/study drug to be dispensed for the participant at that visit (as per the HPTN 046 prescription).
  - When RE-SUPPLY is marked, open-label NVP/study drug will be dispensed for the participant in the quantity entered on the slip.
  - When HOLD is marked, open-label NVP/study drug will not be dispensed for the participant unless/until another slip marked RESUME is subsequently completed and received in the pharmacy.
  - When RESUME is marked, a previous hold will be ended and open-label NVP/study drug will be dispensed for the participant in the quantity entered on the slip.
- Record the scheduled visit week or month for which the Pharmacist is to dispense open-label NVP/study drug.

- The clinic staff name, signature, and signature date must be completed by a clinic staff member authorized to order open-label NVP/study drug for participants during follow-up. DAIDS does not require that an authorized prescriber sign and date Open-label NVP/Study Drug Request Slips; however site-specific pharmacy regulations may be more stringent than DAIDS requirements. All sites must comply with local requirements.
- Double-check the accuracy of all entries and then separate the two parts of the completed Open-label NVP/Study Drug Request Slip. Retain the yellow copy in the participant study notebook. Deliver the white original to the study pharmacy in the same manner that original prescriptions are delivered to the pharmacy. Both the original and clinic copy of the slip may be hole-punched.

Figure 8-13. HPTN 046 Open-Label NVP/Study Drug Request Form

<b>Clinic:</b>	
----------------	--

**Infant's Participant ID Number:**

--	--	--	--	--	--	--	--	--	--

**Kit ID Number:**

--	--	--	--	--	--

**Date of Birth:**

--	--	--	--	--	--	--	--

DD                      MMM                      YY

**Clinic Staff Instruction:** Mark whether this is a drug re-supply, hold, or resume request. Record visit week/month, number of bottles to be dispensed (if applicable), and sign and date. Deliver top copy to pharmacy. File bottom copy in participant research record.

**RE-SUPPLY** → **Pharmacy:** Dispense  bottles of open-label NVP/study drug (20 mL/bottle) for participant as directed on prescription.

**HOLD** → **Pharmacy:** Do not dispense open-label NVP/study drug for participant unless/until another Product Request Slip marked "RESUME" is received.

**RESUME** → **Pharmacy:** Dispense  bottles of open-label/study drug (20 mL/bottle) for participant as directed on prescription.

Comments \_\_\_\_\_

Clinic Staff Name (please print): \_\_\_\_\_

Clinic Staff Signature: \_\_\_\_\_

For Visit:  week **OR**  month

Date:  -  -   
DD                      MMM                      YY

Sites can choose to complete the Open-label NVP/Study Drug Request Slip to order infant packets for individual participants in advance of the infants' scheduled visit. The infant packets will include the requested supply of 30 mL bottles containing 20 mL of open-label NVP / study drug to last until the next visit, pre-marked syringes, and a dispensing slip (for sites at which the

clinic staff give the open-label NVP/study drug to the mother). Upon the receipt of a completed Open-label NVP/Study Drug Request Slip, the pharmacist may prepare infant packets using instructions in the *HPTN 046 Pharmacist Study Drug Management Procedures* prior to the infant's scheduled visit. Prepared infant packets must be stored at controlled and continuously monitored and recorded temperatures (15°-30°C) in a locked, limited access area in the study clinic or in the pharmacy. See Section 8.4 for additional storage requirements. For sites that will store the packets in the clinic, designated clinic staff should request these packets from the pharmacist at least one business day (i.e., 24 hours or more) prior to picking them up from the pharmacy. If an Open-label NVP/Study Drug Request Slip has been completed for a participant in advance of a visit and the clinician determines that the infant is not eligible for continued dosing or needs to have his/her dose held, a second Open-label NVP/Study Drug Request Slip must be completed indicating the hold. This request slip should be sent to the pharmacist as soon as possible, and the infant's mother will not be given any study drug at that visit. The pharmacist will file the request slip using instructions in the *HPTN 046 Pharmacist Study Drug Management Procedures*.

If for any reason a clinician does not want the pharmacist to dispense the number of bottles stated on the original prescription, authorized clinic staff must document the actual quantity to be dispensed ("re-supplied") on the Open-label NVP/Study Drug Request Slip with a note of explanation added to the comments field. For example, an infant receiving open-label NVP will not need two bottles of NVP at their 5 week visit if they come to the clinic at 39 days of age. In this scenario the comment could be written "39 days of age". (*Note: Bottles dispensed by the pharmacist will always contain 20 mL of open-label NVP/study drug*).

If a mother tells the clinic staff that she and her infant will be out of the area on the target date for a subsequent follow-up visit but is able to schedule another date within the infant visit window, clinic staff should notify the pharmacist of this actual scheduled visit date using the Open-label NVP/Study Drug Request Slip and work with the pharmacist so the mother can be given an extra supply of open-label NVP/study drug and oral syringes if needed. The additional quantity of open-label NVP/study drug bottles and syringes should be indicated on the slip and a note added to the comments field.

If a mother tells the clinic staff that she and her infant will be out of the area for a subsequent follow-up visit and unable to return to the clinic within the infant visit window, clinic staff should notify the pharmacist by marking HOLD on the Open-label NVP/Study Drug Request Slip and adding a comment as to the reason (i.e., unable to return within infant visit window). (*Note: See Section 6.2.2 and 6.2.3 of HPTN 046 regarding resuming therapy.*) No open-label NVP/study drug will be dispensed at this visit.

### **Non-Scheduled Visits**

Clinic staff should use the HPTN 046 Study Drug Request Slip (Figure 8- 13) to communicate to pharmacy staff that a participant needs additional study product and/or oral syringes to last until the next scheduled/re-scheduled visit (as long as that visit is within the infant's visit window).

#### **8.7.2 Dispensing of Pharmacist Prepared Infant Packets (Open-Label NVP or Study Drug) at Follow-up by Clinic Staff to Mothers**

If the infant packet is given to the mother by designated individuals at the site after preparation by the pharmacist, the HPTN 046 Record of Receipt of Infant Specific Packets (Figure 8-4) must be used to document dispensing of packets (containing open-label NVP/study drug and oral

syringes) to clinic staff. Pharmacy staff will complete the top section (site name, site number, clinic name) and the first five columns on the Record of Receipt. When receiving packets from the pharmacy, clinic staff will verify the PTID, confirm the number of 30 mL bottles (containing 20 mL of open-label NVP/study drug), confirm the number and size of the oral syringes, and complete the remaining three columns for each PTID. Comments may be recorded in the designated column and on the back of the record if additional space is needed. All Records of Receipt will be retained in the pharmacy.

It is the responsibility of the dispenser to ensure that the pharmacist has completed all of the information on each part of the infant packet label (Figure 8-14) and the open-label NVP/study drug bottle label (Figure 8-7) with the exception of the date of dispensing, which will be added by the dispenser. It is also the dispenser's responsibility to verify that the infant's participant ID number (PID) and the dose to be administered for that visit window are accurate and that the syringes are marked correctly. Prior to giving the infant packet to the mother, the dispenser will obtain the 30 mL bottles and tear off the removable portions of the label from each bottle. One label from each bottle of open-label NVP or study drug will be placed on study source records. The additional label from each bottle of study drug will be adhered to page 2 of the Infant's Study Drug Dosing (IDD-2) DataFax form if the infant has been randomized or to the back of the dispensing slip in the infant is not yet randomized.

The dispenser will complete the HPTN 046 Dispensing Slip (Figure 8-15) included in the packet by adding the infant participant ID number, date of dispensing, and his/her initials. The dispenser will add the dispensing date to the infant packet label (Figure 8-14) and attach the completed right portion of the label to the HPTN 046 Dispensing Slip in the area indicated.

Dispensing slips should be returned to the pharmacy by the end of the day on which dispensing occurred. Slips must be returned within 5 working days of dispensing. A pharmacist will not be able to dispense any additional open-label NVP/study drug for an infant participant if the dispensing slip has not been completed appropriately and sent to the pharmacy. The dispensing slip and original open-label NVP/study drug request slip must be kept in the pharmacy.

**Figure 8-14. Infant Packet Label**

HPTN 046	HPTN 046 Open-label NVP/ Study Drug
PID#: _____	PID#: _____
Kit ID#: _____	Kit ID#: _____
<b>To be dispensed at week 2 visit</b>	Dispensed at week 2 visit on: _____ Date (dd-mmm-yy)
	<b>*Complete label and Attach to clinic dispensing sheet and return to pharmacy*</b>

**Figure 8-15. HPTN 046 Dispensing Slip - Week 2 Visit**

Attach label from outside of Infant's Week 2 Packet here	Dispensed to Infant PID #: _____ On: _____ By: _____
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In the event that an infant-specific packet is dispensed to the clinic in advance of a participant's visit, but the packet is not given to the infant's mother (e.g., the infant is not eligible for continued dosing, the mother/infant pair misses the visit, etc.), the infant packet must be returned to the pharmacy. The HPTN 046 Record of Return of Infant Specific Packets (Figure 8-5) must be used to document the return of infant-specific packets (containing open-label NVP/study drug and oral syringes) to pharmacy staff. Clinic staff will complete the top section (site name, site number, clinic name) and the first five columns on the Record of Receipt. When receiving infant specific packets back from the clinic, pharmacy staff will verify the infant's participant ID number (PTID), confirm the number of 30 mL bottles (containing 20 mL of open-label NVP/study drug), confirm the number and size of the oral syringes, and complete the remaining three columns for each infant's participant ID number (PTID). Comments may be recorded in the designated column and on the back of the record if additional space is needed. All Records of Return will be retained in the clinic.

### **8.7.3 Dispensing Open-Label NVP/Study Drug (Infant Packets) at Follow-up by Pharmacist Directly to Mothers**

For sites where women will return to the pharmacy to have their infant's prescription filled at follow-up visits, designated staff should complete the Open-label NVP/Study Drug Request Slip and/or any other documents required by the pharmacist and send them with the woman to the pharmacy. An SOP must be available regarding this process. Prior to giving the infant packet to the mother, the pharmacist will obtain the 30 mL bottles out of the packet and tear off the removable portions of the label from each bottle. The labels will be set aside and one label from each bottle of open-label NVP or study drug will be placed on study source records. The additional label from each bottle of study drug will be adhered to page 2 of the Infant's Study Drug Dosing (IDD-2) DataFax form for infant's that are randomized or to the back of the dispensing slip in the infant is not yet randomized.

The pharmacist will add the dispensing date to the infant packet label (Figure 8-14) and attach the completed right portion of the label to an infant participant specific dispensing log which will be kept in the pharmacy (refer to *HPTN 046 Pharmacist Study Drug Management Procedures*).

## **8.8 Administration Instructions (Open-Label NVP and Study Drug) for Mothers**

The following instructions will be given to and demonstrated for all mothers whenever study drug is given:

- Gently shake the open-label NVP/study drug by inverting the bottle several times. The bottle should not be shaken vigorously.
- Remove cap from bottle.

- A new oral syringe should be placed into the Press-In Bottle Adapter (PIBA) and the suspension drawn up to the pre-marked dosing line.
- The open-label NVP/study drug should be given to the baby at the same time each day (or as close to the same time as possible), e.g., first thing in the morning.
- If a mother forgets a dose at the regular time, she can give the late dose on the same day until the infant's bedtime. She should not make up the dose the following day by giving two doses at one time. Doses should never be doubled.
- If the baby vomits within 60 minutes of open-label NVP/study drug dosing, the baby may be re-dosed one time following the first dose.
- Used syringes should be discarded and a new syringe must be used for each dose given to the infant. Syringes can be disposed of by mothers or can be returned to the clinic for disposal by the study staff.

Mothers will also be informed of the following storage requirements:

- The bottle should be recapped and tightly sealed immediately following each use.
- The bottle should be stored at 15° - 30°C.
- The bottles should be brought back to the clinic at the next visit. (*Note: These bottles should be returned to the Pharmacy as soon as possible. Clinic staff should not measure or record the amount of study drug returned.*)