Post-exposure Prophylaxis (PEP) Pilot Program (P-QUAD)

Version 4.0

A Pilot Project to Operationalize the Prevention Strategy of Post-exposure Prophylaxis following Sexual Exposure to HIV in combination with Educational Programming & Behavioral Risk Reduction Strategies in Los Angeles County

A Treatment Program

Sponsored by:

Los Angeles County Office of AIDS Programs and Policy,
UCLA Center for HIV Identification, Prevention, and Testing (CHIPTS), UCLA Center for Clinical AIDS Research & Education (CARE),
and
AIDS Project Los Angeles (APLA)

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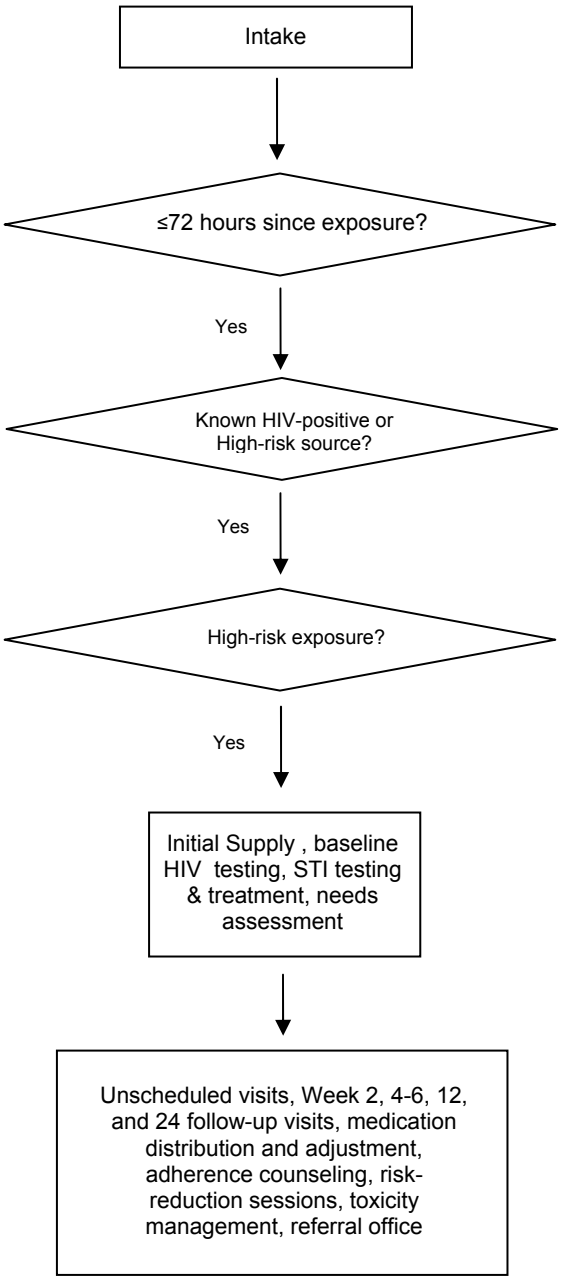

Intake
≤72 hours since exposure?
Yes
Known HIV-positive or High-risk source?
Yes
High-risk exposure?
Yes
Initial Supply , baseline HIV testing, STI testing & treatment, needs assessment
Unscheduled visits, Week 2, 4-6, 12, and 24 follow-up visits, medication distribution and adjustment, adherence counseling, risk-reduction sessions, toxicity management, referral office

1. Program Background and Rationale

As of 2006, approximately 20,000 persons living with AIDS reside in Los Angeles County, and approximately 1,000-1,500 new AIDS cases are reported yearly.[1] National estimates indicate that 25% or more of persons infected with HIV are likely unaware of their diagnosis, highlighting routine and destigmatized HIV testing as a cornerstone of any HIV prevention effort, and estimates of annual new HIV infections nationwide have stabilized at approximately 40,000 new infections per year.[2]

In Los Angeles County, HIV infection is largely associated with male-male sexual contact (76% of cases), with only 7% of AIDS cases attributable to injection drug use,[3] suggesting the central role of sexual behaviors in the local HIV epidemic. Los Angeles County has the second highest concentration of AIDS cases nationwide[4] despite ongoing prevention efforts. While no single prevention modality will realistically confer 100% protection against HIV infection, a combination of behavioral risk-reduction programming, mental health and substance abuse referral services with novel biomedical technologies is an attractive multidisciplinary programmatic approach to HIV prevention.

Post-Exposure Prophylaxis (PEP) after sexual exposure to HIV is recommended by the Centers for Disease Control and the California State Office of AIDS.[5-6] Although no efficacy data exist for PEP after sexual exposure, strong analogy is made to experience in related fields:

Post-exposure prophylaxis for occupational exposures to health-care workers (HCW, for example needlestick injuries) has been demonstrated in a single case-control study to reduce the odds of acquiring HIV after a needlestick injury from an HIV-positive source participant by 81% (OR 0.19, 95% CI 0.06 to 0.52).[7] The baseline risk of acquiring HIV after a needlestick from an HIV-positive source participant is approximately 0.3%.[8]

The standard of care in the developed world for the prevention of mother-to-child transmission of HIV includes maternal treatment during pregnancy, intrapartum, and newborn treatment post-partum. Such regimens were initially demonstrated to reduce the risk of vertical HIV transmission from 25.5% to 8.3%.[9] Clearly, not all HIV-infected pregnant women will be diagnosed with HIV and in appropriate antenatal care at the time of their delivery. New York State, which has employed mandatory HIV-testing by PCR of all newborn infants, has documented that while maximal benefit is indeed achieved in transmission reduction when all 3 “periods” of parturition are “covered” with antiretroviral treatment (ART), substantial benefit can still be achieved if ONLY the infant is treated post-partum (within 48 hours of delivery, RR 0.35 [95%CI 0.19-0.65]), in a “post-exposure” capacity.[10]

With the above observations and additional animal model data, it would currently be both unethical and infeasible to conduct a randomized placebo-controlled RCT to demonstrate efficacy of PEP after sexual exposure. Despite the impressive reductions in HIV acquisition demonstrated in these related situations, PEP after sexual exposure has received surprisingly limited uptake among both providers and consumers of HIV prevention services. PEP after sexual exposure to HIV has been demonstrated to be safe, feasible, and cost-effective if appropriately targeted.[11-12] The majority of this experience has been in men who have sex with other men (MSM).[13-15]

Details with regard to appropriate candidacy for PEP, optimal treatment regimens, timing, follow-up procedures, and concomitant services to be offered are largely based on expert recommendation in the absence of definitive data.

1.1. Rationale for Source Participant Characteristic Candidacy Criteria

It is clear that a verifiably negative source participant confers no risk of transmitting HIV to an exposed participant. It is similarly clear that a documented HIV-positive source participant carries a real potential to transmit their HIV to an exposed participant. Often, the source is of unknown HIV serostatus (either unknown to the source him/herself or unknown by the exposed participant, regardless of source self-knowledge).. Therefore, experts and guiding bodies have found utility in stratifying sources into dichotomous categories: Sources of sufficient risk to warrant consideration for prophylaxis, and sources of insufficient risk to warrant consideration for prophylaxis. While ultimately governed by local epidemiology, it is reasonable to classify subjects from the following risk groups as of sufficient risk to warrant consideration for prophylaxis:

Men who have sex with men (MSM)
Men who have sex with men and women (MSM/W)
Injection drug users (IDU)
Commercial Sex Workers (CSW)
Persons who have a history of incarceration
Known to be HIV infected
From endemic country (baseline prevalence >1%)
Perpetrator of sexual assault
Sex partners of any of the above categories

These categories derive from national and local epidemiology of highest HIV-seroprevalence populations.

1.2. Rationale for Type of Exposure Candidacy Criteria

1.2.1. Route of Exposure

Initial cost-effectiveness studies suggested limitation of cost-efficacy to only receptive anal intercourse (RAI) with known HIV-positive partners.[16] However, subsequent analyses demonstrated cost-effectiveness when programs were limited to "high risk" exposures which included RAI, insertive anal intercourse (IAI), receptive vaginal intercourse (RVI), and insertive vaginal intercourse (IVI).[11-12] Most guidelines additionally classify receptive oral intercourse *with* intra-oral (or mucosal) ejaculation with the above listed "high risk" categories, although data regarding precise risks attributable to oral intercourse have remained elusive.

1.2.2. Material Composition of Exposure

While by highly sensitive laboratory techniques, the presence of HIV has been confirmed in a wide variety of bodily fluids[17] only blood, genital secretions, breast milk, or other *visibly bloody* body fluids are considered of sufficient risk of accomplishing transmission to warrant consideration of prophylaxis.[6]

So as to address the many permutations of high-risk routes of exposures to high-risk source materials and allow for clinician judgment, many guidelines have a general inclusion criteria encompassing visibly bloody body fluids, blood, breast milk, or genital secretions from a high-risk or known positive source in contact with mucous membranes (including but not limited to genital and oral mucosa) or non-intact skin. These "catch-all" categories must be employed judiciously in order to preserve the cost-efficacy of the intervention.

1.3. Rationale for Timing Candidacy Criteria

Animal models of post-exposure prophylaxis suggest that after exposure, there is a finite "window-of-opportunity" during which attempts to abort infection is likely to be successful. The precise duration of such a "window-of-opportunity" is unknown, but expert opinion and guidelines recommend that the "exposure-to-ingestion" time for first dose of PEP, if appropriate, be as short as possible.

Macaque models suggest persistent benefit after 24 hours post-exposure[18-19] New York State has the most conservative cut-off recommendation at 36 hours; most other state, national, and international guidelines recommend consideration for PEP extend to 72 hours post-exposure[6,20-24].

While it is true that the timing post exposure after which there is no benefit to treatment is unknown, routine consideration beyond 72 hours post exposure is discouraged. Although the protocol provisions for a 72 hour eligibility, it is clear that PEP should be administered AS QUICKLY AS POSSILBE after exposure.

1.4. Rationale for Treatment Regimens

The most clinical efficacy and safety experience in the PEP realm resides with the fixed-dose combination of zidovudine and lamivudine (marketed as Combivir®). This combination of two nucleoside-analogue reverse transcriptase inhibitors (NRTIs) is administered as one tablet orally twice daily.

The toxicity of the zidovudine component of Combivir confers headaches, nausea, asthenia, as well as, anemia, granulocytopenia, and liver function abnormalities. Truvada® (a fixed dose combination of tenofovir disoproxyl fumarate and emtricitabine) has achieved preferred status over Combivir for the treatment of chronically infected HIV participants, and has had limited but encouraging reports of use in the post-exposure prophylaxis literature.[25-26]

Experts disagree regarding whether 2 agents (such as the dual-NRTI combinations above) is sufficient prophylaxis or if a third agent should be added in select, or all cases.

Proponents of 2-agent therapy argue that the inoculum of HIV after an exposure is orders-of-magnitude smaller than that encountered in chronic HIV infection, therefore it is likely that dual therapy, while clearly insufficient to treat chronic infection, may be more than adequate to abort infection from such a small viral population. They further argue that the additive toxicity accrued from the addition of a third agent is accompanied by dramatically increased rates of toxicity, and both endangers tolerability and completion rates (see below)[27], and is not cost effective. They further point out that there is no data in the exposure literature demonstrating that 3-agent combinations are superior to 2-agent combinations, or for that matter, single agent therapy.

Supporters of 3-agent therapy note that while there is paucity of data on relative efficacy of 3-agents vs. 2-agents, general consensus among the HIV-treatment community is that 3-agents provides the optimal balance of efficacy and toxicity in chronic HIV infection – therefore anything else might be considered suboptimal therapy. In the event of a "true" exposure, where the dichotomous outcome for an individual is "infected" or "uninfected," there is little justification for use of less than "optimal" therapy. They further argue that the modern improved tolerability of 3-agent combinations make arguments of increased toxicity obsolete, or at least insignificant. Mathematical modeling suggests cost-efficacy of the use of 3-agent combinations if the baseline prevalence of transmitted resistance in the local epidemiology is >15%,[28] which is approximated in many urban centers in the United States. Some data from heterosexual transmission additionally suggest that

a single virus or a small founder population of viruses are responsible for propagating the transmitted infection,[29] and therefore multi-class therapy (i.e. 3 drugs) may be preferred to cover potentially resistant species.

Guidelines have addressed this lack of consensus in different ways: The CDC has recommended use of 2-NRTIs for high risk exposures (a "standard" PEP regimen), and reservation of 3-agent treatment for the highest-risk category of exposures (an "expanded" PEP regimen) including receptive anal intercourse with a known HIV-positive partner, and any inclusory exposure in which viral resistance may an issue. The choice of third agent is generally agreed upon as a boosted protease inhibitor, such as lopinavir/r (Kaletra®). Currently, available NNRTI-based regimens are to be avoided: nevirapine due to hepatotoxicity and efavirenz due to susceptibility in the face of transmitted resistance as well as teratogenicity in women who may become or desire to become pregnant.

Raltegravir has rapidly been established as a first line treatment component in both treatment naïve and treatment experienced HIV-infected patients.[30] Experience with the use of this agent in post-exposure prophylaxis is increasing; case reports and case-series-level data support the safety and impressive tolerability of this agent in a prophylactic capacity.[31]

The use of some novel agents, such as maraviroc, while mechanistically attractive, have only case-report/case-series level data in the medical literature to support use; more general implementation of such agents and novel classes in PEP regimens may be premature.

1.5. Rationale for Duration of Treatment

Based on macaque and *in vitro* data, post-exposure prophylaxis treatment should be continued for 28 days. Animal data suggest that shorter courses of 3 or 10 days are less effective.[18-19] Other intermediate durations of treatment and longer durations have not been formally studied and cannot be endorsed nor should they be considered outside a study context.

1.6. Rationale for Concomitant Services

The psychology of risk-taking behavior is enormously complex, and such discussion is outside the purview of this protocol; however, it has been noted that changing behaviors is one of the most challenging components of any medical treatment program.

Risk-reduction behavioral programming and other behavioral interventions have had mixed results in accomplishing long-term benefit in terms of reduced HIV and STI acquisition.[32] Recent studies have demonstrated incremental benefit of more intensive risk-reduction programming compared to standard counseling for highest-risk participants.[33]

The high rate of concomitant substance use, especially stimulant use, associated with high-risk sexual behavior and the success of novel technologies such as contingency management (CM) combined with cognitive techniques makes facile referral to such services a logical partnership for appropriate participants.[34]

The need for mental health referral for a variety of mood and personality disorders often parallels the need for substance abuse services, and referral to such services must be similarly seamless and part of a prevention package offered.[35-37]

Adherence counseling is imperative in the success rates for completion of PEP courses.[13] Such counseling addresses not only issues of compliance to dosing, but

often pre-emptively manages toxicity, and can be accomplished with trained pharmacy staff and/or mid-level practitioners.

Intensive and proactive follow-up has been shown to be paramount in achieving follow-up and retention, including letters, telephone calls, and if applicable cell-phone text message and email reminders.[13-15,38-39]

2. Program Design

The Los Angeles County P-QUAD program is a combined effort of County, City, public health, community, academic, and private agencies and individuals in an effort to provide a comprehensive package of HIV prevention services of which PEP can be an integral component. These services are designed to be easily accessible, non-judgmental, culturally, ethnically, and linguistically appropriate to the relevant populations, community-based, and independent of ability to pay or insurance/documentation status. They will also provide vital linkages to associated services, routine HIV testing, and primary health care.

In its initial pilot project, 2 community-based sites will serve as facilities at which participants may present for screening for post-exposure prophylaxis services, as well as sexually transmitted diseases. At the sites, initial eligibility and testing will be performed, and an initial 14-day supply of PEP medications will be provided if appropriate, and referrals will be initiated. All subjects who are provided an initial 14-day supply will be required to return to the site for the remainder of the 28-day course of medication, follow-up testing, adherence counseling, risk-reduction programming, and other appropriate referrals. Follow-up with participants by phone, email, and mobile-phone text message will be used as appropriate to maximize program retention.

If successful, future expansion of the program will entail progressively more extensive and localized/specialized/customized sites which will be more neighborhood-based.

Secure data forms will allow confidential P-QUAD staff access to records, plans, and referrals which will hopefully serve as a database to serve future research needs and promote ongoing programmatic improvement.

3. Enrollment of Participants

3.1. Inclusion Criteria (All must be satisfied)

Participants must be at least 18 years of age
Able to understand and provide consent
High-Risk Exposure Characteristic
(one or more of the below, unprotected or with failed condom use)
Receptive Anal Intercourse
Insertive Anal Intercourse
Receptive Vaginal Intercourse
Insertive Vaginal Intercourse
Receptive Oral Intercourse with Intraoral Ejaculation *with known HIV+ source*
(supersedes all “high-risk source” criteria below)
Sharing injection drug works which have been intravascular
High-Risk Source (one or more of the below)
Known HIV positive
MSM
MSM/W
IDU

CSW
Sexual perpetrator
History of incarceration
From an endemic country (prevalence >1%)
Partner of one of the above

Exposure within 72 hours of presentation
Not known to be HIV positive
No countermanding concomitant medications or allergies

---------- If above inclusion criteria are met, administer 1st dose----------
HIV-negative on presentation and without symptoms of PHI (do not withhold first dose pending these laboratory assessments). For management of suspected PHI, see **Section 6.4.**

3.2. Exclusion Criteria

Participants <18 years of age
Unable to understand and provide consent
Exposure >72 hours of presentation
Known to be HIV positive
Any condition, which in the opinion of the intake provider, will seriously compromise the participant's ability to comply with the protocol, including adherence to PEP medication dosing
Demonstrated HIV-positive on rapid testing
Unwillingness to commit to barrier-method (male and/or female condom) use until HIV-negative-status is confirmed 6 months after exposure
Unwillingness of breast-feeding women to transition to formula feeding

If the participant presents with symptoms consistent with PHI, a 3-drug regimen may be provided pending appropriate laboratory confirmation and referral. 2-drug regimens should NOT be used in such settings. Such subjects should be referred to expert HIV clinical care immediately for further evaluation and treatment.

3.3. Program Enrollment Procedures

Enrollment may only be initiated in person. To enroll, a participant presents to one of the two P-QUAD site facilities. An intake of inclusion and exclusion criteria will be performed by program personnel. HIV-testing and STI testing will be provided as well as a brief and directed history and physical examination. If all inclusion and no exclusion criteria are met, an initial dose of PEP medications will be provided for immediate ingestion. A 14-day supply of PEP medications will be provided. Participant information sheets regarding PEP will be provided. Initial safety laboratory measurements and assessment of necessary referral services will be made, and behavioral risk assessment will stratify participants into "moderate behavioral risk," or "high behavioral risk." Moderate risk participants will receive risk-reduction programming within the P-QUAD program; high-risk participants will be referred externally to existing LA County behavioral risk-reduction programming. Enrollment will be charted on **Form A**.

3.4 Participants who have begun PEP via a starter-course obtained at another institution

Participants currently in progress of a course of PEP obtained through non-PQUAD mechanisms MAY be included with the permission of BOTH the site PI AND either a) the program PI or b) the OAPP medical director, if the program PI is unavailable.

Such participants will not be considered for P-QUAD participation if they have been on therapy for longer than 7 days, or if they have more than a 72 hour hiatus from their last dose of antiretroviral medication. They must go through the P-QUAD informed consent process, and complete baseline assessments and procedures at program intake.

In such cases, participants will be provided with sufficient medication to last until the regularly scheduled Day 14 visit, after which time regular protocol procedures will be followed subsequently.

Screening will use the Alternate Screening Form, and if eligible, will be charted on **Form A.**

4. Program of Treatment

Year 1 of the program will plan to treat 100 participants.

4.1. Regimens, Administration, and Duration

The preferred regimen for standard, high-risk exposures will be tenofovir + emtricitabine, provided as a fixed-dose combination tablet as Truvada®. Dosing of Truvada is 1 tablet by mouth once daily. For partipicants with a creatinine clearance 30-49 mL/min, dosing of Truvada is 1 tablet by mouth every other day. For participants with creatinine clearance <30 mL/min or on hemodialysis, Truvada should not be used. For intolerance to Truvada, pregnancy, or in the event of Truvada non-availability, Combivir (zidovudine 300mg/lamivudine 150mg) will be available to be taken as 1 PO BID.

For highest-risk category exposures (receptive anal intercourse with a known or suspected HIV-positive source participant or in cases of suspected source drug resistance, see Schema, below) one of the following should be added to the above "standard" treatment, creating an "expanded" regimen:

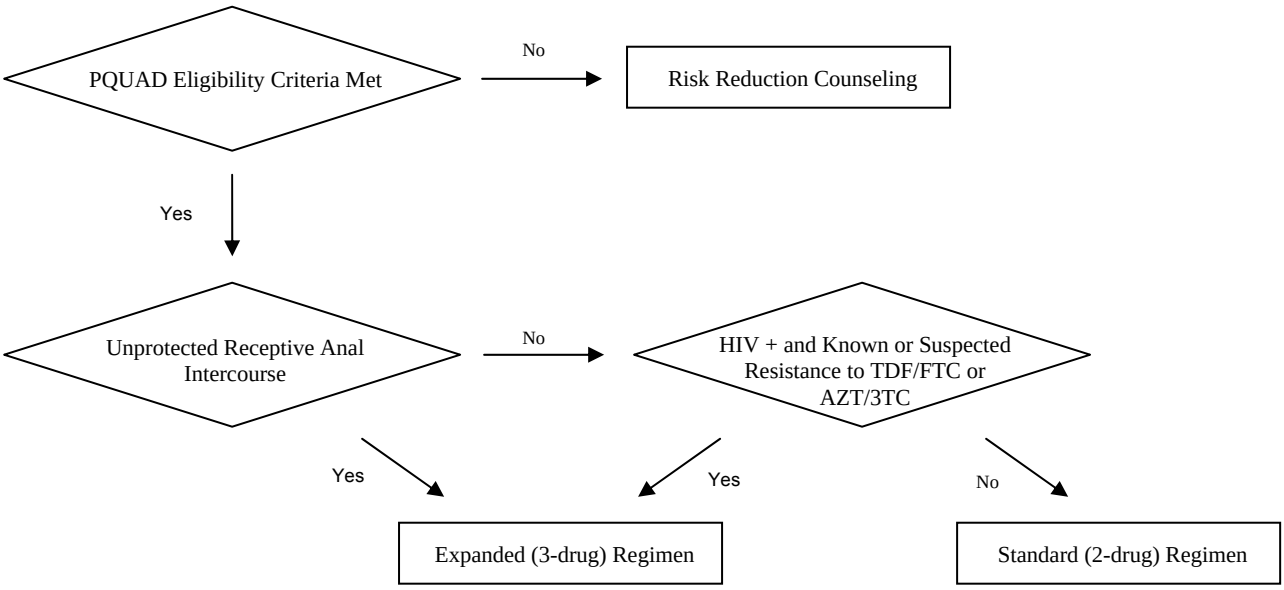
Preferred: Lopinavir/ritonavir (200mg/50mg), 2 tablets orally twice daily or 4 tablets once daily

Preferred/Alternative: Raltegravir 400 mg, 1 tablet orally twice daily

The above additions to the "standard" regimen should be taken with food. Components of "expanded" regimens should not be dose-adjusted for renal insufficiency.

If source resistance is suspected or known, *expert HIV consultation should be sought, but ANY DELAY IN ADMINISTERING A FIRST DOSE OF AN "EXPANDED" 3-DRUG REGIMEN IS DISCOURAGED. The regimen may be adjusted subsequent to a first dose after consultation with experts.*

In the event of toxicity, intolerance, or allergy, see Toxicity Management, below, **section 7.1.**



Missed dose instructions

A missed dose should be taken if the discovery of the missed dose is within 6 hours of the intended dose-time. If the discovery of the missed dose is longer than 6 hours from the intended dose-time, the dose should not be taken, and dosing resumed at the next intended dose-time. Doubling of dosing should not occur.

Duration of therapy

All regimens should be taken for 28 days. For participants who are on every-other-day dosing schedules, this may total fewer than 28 individual days on which medication doses are ingested, but will still compose 28 days of medication exposure from the date of first dosing PEP medications.

4.2. Drug Supply, Distribution, Accountability

Truvada (emtricitabine 200mg/tenofovir 300mg) will be available in bottles of 30 tablets to be taken as 1 PO QD. For intolerance to Truvada, a limited supply of Combivir (zidovudine 300mg/lamivudine 150mg) will be available in bottles of 60 tablets to be taken as 1 PO BID.

For expanded regimens, Kaletra (lopinavir 200mg/norvir 50mg) will be available in bottles of 120 tablets to be taken as 2 PO BID (or 4 PO QD); Raltegravir (Isentress) will be available in bottles of 60 tablets to be taken as 1 PO BID. For intolerance to Kaletra or raltegravir, the alternative agent should be used.

Site pharmacies will be responsible for dispensing 15-days of appropriate medication at the initial and day 14 visit, in appropriate packaging based on manufacturer's instructions (USP equivalent tight containers for Kaletra Tablets and Truvada Tablets). Pharmacies at sites will be responsible for documentation of all medication dispensing and tracking of all program-related medications.

Participants *must* follow-up the site to receive the remaining treatment course and associated testing and services. At the 14-day time point, participants will receive their second and final supply of 15-days of PEP medication, appropriate laboratory testing, and adherence counseling.

Further 15-day supplies will *not be re-dispensed* in the event of medication supply loss or destruction. All other medication replacements will be at retail cost.

4.3. Concomitant Medications

Concomitant medications will be assessed at initial intake, and recorded on **Form A**. Concomitant medication lists will be reviewed by program pharmacy staff, and flagged for potential drug interactions as appropriate, and triaged on a 2-tier system of Severe (which will trigger a phone contact to the participant within 24 hours of registration) or Limited (which will be followed up on upon at next visit).

All subjects will be counseled that condoms should be used for all forms of genital-genital sexual contact pending results of the 6-month (24 week) follow-up HIV testing results.

Because of concerns that boosted-PI-containing PEP regimens render oral contraceptives less effective, subjects shall be instructed that oral contraceptive pills (OCPs) may be inadequate to prevent pregnancy during PEP regimen administration, providing further impetus for barrier contraceptive use.

4.4. Adherence Assessment and Intervention

At each study visit, adherence will be assessed by 4-day participant recall as well as pill count. Participants will be required to bring in remaining drug supply at each visit for pill counting.

All participants will receive initial adherence counseling and an information/education sheet regarding adherence at program entry.

Participants will have one subsequent formal session of adherence counseling at the time of dispensing of the second 14-day treatment supply.

Based on initial assessment, participants will have a tailored adherence plan which may include some or all of: Regular telephone contact, email reminders/contact, and cell-phone text message reminders/contact. The plan will be revisited at the day 14 adherence counseling session, and the adjusted plan will be continued through the end of the treatment course.

Contact will be maintained in the form of paper mail, telephone, email, and/or text-message as appropriate for regularly scheduled follow-up at the completion of medical treatment (4-6 weeks post-exposure), 12 weeks post-exposure and 24 weeks post exposure.

4.5. Risk Assessment, Drug and Alcohol Assessment, and Risk Reduction Intervention

At the program site intake visit, a risk assessment will be made using a standardized tool, used in HPTN 052 and other large clinical trials. Participants will be risk stratified in a dichotomous fashion into 2 risk groups based on aggregate score in the risk assessment. Data suggest that the highest risk participants require more extensive risk reduction education than do most others. Therefore the highest risk group participants will be referred to existing county-funded behavioral counseling programming. All will be provided a standard risk-reduction counseling brief session with the intake and day 14 visits.

Risk assessments will be done in follow-up at each subsequent HIV-testing points at 4-6 weeks, 12 weeks, and 24 weeks post exposure.

A one time drug and alcohol use inventory will be completed. Any score of "moderate" on the NIDA-modified ASSIST inventory will be considered for substance use referral, and all scores of "high" will be categorically referred for substance use referral.

5. Schedule of Clinical and Laboratory Evaluations

	Baseline (Day 0)	Week 2 Visit (Day 10-14)	Week 4-6 Visit	Week 12 Visit	Week 24 Visit
Meds Dispensed	X	X			
HIV ELISA[c]	X		X	X	X
Urine GC/CT Rectal GC/CT Pharynx GC	X				
Serum RPR	X			X	
Urine HCG[a]	X	X[b]	X[b]	X[b]	X[b]
HBsAg	X				
Cr, LFTs, CBC	X	X[b]			
HIV RNA					
HIV Genotype					
Stored Plasma[d]	X		X	X	X
Adherence Cnsl	X	X			
Drug and Alc Assess	X				
Risk Assess	X		X	X	X
Risk Red (Standard)	X	X			
Referral to Behavioral Programming (Expanded)	X				

[a]Females of childbearing potential only
[b]If clinical signs and symptoms direct, not routine
[c]Positive or indeterminate rapid HIV ELISA testing will be confirmed with a serum Western Blot
[d]Plasma will be drawn and stored at indicated time points. If seroconversion to HIV occurs, these samples will be run for HIV RNA (viral load) and genotyping

5.1. HIV Testing

5.1.1. HIV Laboratory Testing

Rapid ELISA testing will be used (oral transudate or phlebotomized blood). All positive or indeterminate rapid results will be confirmed by serum Western Blot testing.

5.1.2. Testing of Sources

If a source is available for testing, and is of unknown HIV-serostatus, the source should be consented for HIV antibody testing (rapid testing, if available), and with rare exceptions, a negative test is sufficient evidence to recommend discontinuation of post-exposure prophylaxis. The source should be contacted by the exposed participant, or if anonymity is desired, via the provided anonymous partner-notification website (in development).

If the *source* is available, and there is suspicion of a *source* having ongoing high-risk behavior such as recent (within the last 4-6 weeks) high-risk unprotected sexual contact or sharing of injection drug works, the source shoud additionally have HIV RNA testing; in such cases, post-exposure prophylaxis of the exposed participant should be continued, and *consultation with HIV treatment experts should be employed.*

Known HIV-positive sources should be queried for longitudinal history of antiretroviral therapy, reasons for antiretroviral changes (i.e. virologic failure or toxicity), CD4 count and viral load history (most current values being most relevant). Hepatitis B and C status, if known should be interrogated. If resistance is known or suspected, *consultation with an HIV expert should be sought* before choice of PEP regimen is made; however if expert consultation cannot be provided immediately, an expanded 3-drug regimen should be implemented as soon as possible, and expert consultation obtained after initial dosing, with subsequent modification as appropriate.

If the source is not available, the exposed participant should be queried as to likely demographic parameters to help program personnel with risk stratification (i.e. MSM, IDU, CSW, endemic national, etc).[40-41]

Data for the source should be recorded on **Form C**.

5.1.3. Testing of Exposed Participants

Concomitant with administration of first doses of PEP, HIV-testing should be performed, preferably rapid HIV-testing. If HIV-negative, but the participant has signs/symptoms consistent with primary HIV infection (PHI), the participant should be referred to expert HIV-providers for further management. If NAAT testing is available at the site at no-cost to participants, this should be sent and noted on **Form A** along with other baseline information. Subjects, as noted below, may be enrolled in the protocol if the suspected exposure meets all inclusion and exclusions criteria for the program – however, a 3-drug regimen is mandated in the case of suspected or confirmed PHI.

If HIV-negative, the protocol is activated. Guidelines differ on the timing and extent of laboratory testing. The current protocol uses California State Office of AIDS laboratory monitoring recommendations, which includes only symptom-directed monitoring during treatment and serial HIV serologic testing out to 6-months post-exposure.[5]

If HIV-positive, participants should be referred to expert HIV-providers for confirmation and further management. 3-drug PEP may be implemented in such participants pending confirmation of the initial HIV ELISA testing. 2-drug PEP should **never** be used in such contexts.

Initial antiretroviral decision will be documented on **Form A ,** the baseline CRF. All female participants of reproductive potential will be tested for pregnancy by urine hCG testing. Refer to **Section 6.2** for details of management of pregnant or breast-feeding participants.

5.1.4. Testing of Exposed Participants who are not eligible or refuse PEP

In the event a participant is not eligible or refuses PEP, rapid HIV testing should be offered, and referral to services for longitudinal follow-up HIV testing in a linguistically, culturally, and financially appropriate primary-care setting should be made.

5.2 Additional Laboratory Testing

5.2.1 STI Screening – All subjects will be screened at baseline for urethral, rectal, and pharyngeal N. gonorrheae and urethral and rectal C. trochomatis infection by NAAT testing, and for T. pallidum (syphilis) by serum RPR testing. Positive results will trigger referral to appropriate private or LA County STD program sites for treatment. Repeat testing for serum RPR will be performed at the Week 12 visit to assess for incubating syphilis acquired at the time of the initial exposure. Intervening signs or symptoms consistent with sexually transmitted infections should trigger referral to appropriate private or LA county STD program services.

5.2.2 Pregnancy Testing – Women of childbearing potential will be tested for pregnancy by urine hCG at baseline, and as clinically indicated throughout the 6 months of follow-up. A positive result should trigger utilization of the Treatment of Pregnant Women protocol in **Section 6.2** and consultation with HIV treatment experts.

5.2.3 Hepatitis B Testing – Treatment with Truvada or Combivir in participants with chronic active hepatitis B (HBsAg positive) has been associated with flares of hepatitis upon discontinuation of treatment. Such participants will be referred to appropriate medical care for monthly liver function testing subsequent to treatment completion for the duration of the 6-months of follow-up.

5.2.4 Serum creatinine will be checked at baseline to determine appropriate medication dosing, and then only in symptom-directed fashion subsequently

5.2.5 Liver function tests (AST [SGOT], ALT [SGPT], LDH, and alkaline phosphatase will be checked at baseline and then only in symptom-directed fashion subsequently.

5.2.6 Complete blood count (hemoglobin, hematocrit, white blood cell count [WBC], differential, and platelet count) will be checked at baseline and then only in symptom-directed fashion subsequently.

6. Clinical Management Issues

6.1. Toxicity

6.1.1. Truvada (tenofovir + emtricitabine)

In the event of intolerance, including but not limited to rash, nausea, vomiting, clinical jaundice, or abdominal pain, an "unscheduled visit" should be made in which a directed clinical assessment and laboratory evaluations including creatinine, liver function tests, and complete blood count with differential are performed. Alternative regimens may be substituted, including Combivir (zidovudine + lamivudine). Note that other combinations are acceptable with HIV expert consultation, but *will not be provided by the program.*.

Dosing of zidovudine + lamivudine (Combivir) is 1 tablet by mouth twice daily. For participants with a creatinine clearance <50 mL/min, including those on hemodialysis, Comibivir may be dose-adjusted to 1 tablet by mouth once daily.

6.1.2. Combivir (zidovudine + lamivudine)

In the event of intolerance, including but not limited to rash, nausea, vomiting, clinical jaundice, abdominal pain, fatigue, dizziness, asthenia, and pallor, an "unscheduled visit" should be made in which a directed clinical assessment and laboratory evaluations including creatinine, liver function tests, and complete blood count with differential are performed. Alternative regimens may be substituted with HIV expert consultation, but *will not be provided by the program.*.

Participants receiving such medications may continue to be followed in the P-QUAD program.

6.1.3. Kaletra (Lopinavir/ritonavir)

In the event of intolerance, including but not limited to rash, diarrhea, bloating, nausea, vomiting, clinical jaundice, or abdominal pain, an "unscheduled visit" should be made in which a directed clinical assessment and laboratory evaluations including creatinine, liver function tests, and complete blood count with differential are performed. Raltegravir may be substituted.

6.1.4. *Raltegravir (Isentress)*

In the event that intolerance, including but not limited to rash, diarrhea, abdominal pain, bloating, nausea, vomiting, clinical jaundice, pancreatitis, depression, or flatulence, an "unscheduled visit" should be made in which a directed clinical assessment and laboratory evaluations including creatinine, liver function tests, amylase, lipase, and complete blood count with differential are performed. Kaletra (lopinavir/ritonavir) may be substituted.

Alternative regimens may be substituted with HIV expert consultation, but will not be provided by the program. Participants receiving such medications may continue to be followed in the P-QUAD program.

6.2. Pregnancy and Breast Feeding

For an exposed participant who is pregnant, consultation with clinical experts is recommended, primarily to assist with toxicity management.

The "standard" regimen should consist of Combivir (zidovudine + lamivudine) dosed as 1 tablet by mouth twice daily.

The “expanded” regimen should consist of Combivir (zidovudine + lamivudine) with lopinavir/ritonavir. Combivir is dosed as 1 tablet by mouth twice daily; lopinavir/ritonavir is dosed as 2 tablets by mouth twice daily.

For an exposed participant who is breast feeding, the participant should be treated as per standard protocol instructions above. The participant should discontinue breast feeding immediately and transition to formula feeding and a pump-and-discard program to reduce the incidence of mastitis.

6.3. Sexual Assault

Most guidelines recommend the offering of PEP medications to survivors of sexual assault.[42-44] General advice includes administration of “standard” regimens for receptive vaginal intercourse (RVI) without mucosal tearing with an unknown-serostatus source, and “expanded” regimens for RVI with mucosal tearing, anal intercourse, or a known HIV-positive source.

In general, adherence and follow-up in such cases has been poor, and referral to appropriate rape crisis, law enforcement, and mental health services is crucial. STI testing and prophylactic treatment as well as emergency contraception for females of childbearing potential should be offered.

6.4. Management of Suspected Acute Seroconversion during PEP treatment (Primary HIV Infection - PHI)

Signs and symptoms of PHI are listed below in Table 1. Should an enrolled participant present with signs and symptoms consistent with PHI, this should trigger immediate referral to HIV specialty care for appropriate work-up. Medications should be continued pending return of laboratory tests, and expert clinician guidance.

Table 1. Frequency of Symptoms and Findings associated with Acute HIV-1 Infection[45]

Symptom or Finding	*% Patients*
Fever	>80–90
Fatigue	>70–90
Rash	>40–80
Headache	32–70
Lymphadenopathy	40–70
Pharyngitis	50–70
Myalgia or arthralgia	50–70
Nausea, vomiting, or diarrhea	30–60
Night sweats	50
Aseptic meningitis	24
Oral ulcers	10–20
Genital ulcers	5–15
Thrombocytopenia	45
Leukopenia	40
Elevated hepatic-enzyme levels	21

7. Criteria for Discontinuation

7.1. Temporary Medication Interruption

Attempts should be made to avoid temporary interruption.

Symptoms should be managed aggressively and proactively in an attempt to avoid discontinuation, provided there is no laboratory evidence of toxicity and the symptoms are mild to moderate. In the event of moderate toxicity with laboratory abnormalities, attempts should be made to transition directly from one regimen to another without interruption. In the event of severe toxicity requiring discontinuation and lack of clarity as to the causative agent, medications should be discontinued and then alternative regimens instituted as soon as clinical and/or biochemical resolution of the toxicity is clearly established. Such decisions will need to be made *in conjunction with experts in HIV clinical care.*

In the event of inadvertent discontinuation due to missed appointments, loss of medication, or other unforeseen circumstances, treatment should be resumed counting the missed days as part of the 28 day treatment course. Treatment should ONLY be reinstituted in the absence of signs/symptoms of PHI (Table 1 above).

7.2. Permanent Medication Discontinuation

Permanent medication discontinuation prior to 28 days of treatment should be limited to participants who withdraw consent, are so advised by HIV-treatment experts, or have severe toxicity to two or more regimens. In the event of sequential toxicity, consultation with HIV-treatment experts should be employed prior to abandonment of treatment efforts.

7.3 Program Discontinuation

Request by the participant to withdraw from the program

Participant, in the judgment of program physicians, is unable to comply with provisions of the protocol in such a way as to be more likely to result in harm to the participant

HIV-positive ELISA or viral load result at any time point. Such subjects will be referred to appropriate private or LA county HIV expert care for follow-up and ongoing evaluation and treatment.

8. Data Collection and Storage

8.1. On-line Protocol

This protocol will be available in hardcopy, PDF, and html format for ease of access to study personnel on the OAPP website.

8.2. Secure Database

Access to the documents will be limited by a locked, secure filing system, with only key study personnel having access, providing maximum security for participant information.

Forms A through **L** will be kept as part of the participant record, as will visit note forms and laboratory results and a complete medication treatment list, attendance at adherence and risk reduction interventions, and documentation of other referrals. All forms related to the study will be available for download on the OAPP website. See the MOPs for details of data collection and reporting.

8.2.1. Records to be kept

8.2.1.1. Screening Form – Eligibility Checklist
8.2.1.2. Alternate Screening Form – Already Initiated PEP
8.2.1.3. Form A – Baseline/Intake Form
8.2.1.4. Form B – Day 14 Follow-up Form
8.2.1.5. Form C – Source Information Form
8.2.1.6. Form D – Week 4-6 Follow-up Form
8.2.1.7. Form F – Week 12
8.2.1.8. Form G – Week 24 / Case Close-out Form
8.2.1.9. Form H - Unscheduled Visit Form
8.2.1.10. Form I – Telephone Contact Form
8.2.1.11. Form J - STI Referral/Treatment Tracking Form
8.2.1.12. Form K – HIV Seroconversion Form
8.2.1.13. Form L – Sexual Risk Behavior Form

8.2.2. Adverse Event Reporting

A provider will be on-call for the program to triage and address toxicity management 8AM to 10PM on weekdays, and 8AM to 5PM on weekends and holidays. Toxicity or adverse events requiring formal evaluation will be seen at program site facilities within 24 hours, except over weekends and holidays, when urgent management issues will require local emergency department resources. All toxicity or adverse event (AE) contacts should be recorded on the appropriate CRFs as well as the line-listing AE forms, SAEs must be reported to the PI according to the MOPs and documented appropriately.

9. Participant Confidentiality

In an effort to maintain confidentiality but allow tracking of public health resources, all program entrants will have a unique patient identifier code based on their study site. A date of birth will be requested from participants to allow 2 methods of identification required for study sample identification.

9.1. Consent Form

The study will be overseen by the UCLA Institutional Review Board, and the study and all related study documents will be approved by the UCLA IRB.

Although PEP is recommended by state, national and international health agencies, the medications used in PEP have not received FDA approval for a preventive/prophylactic indication, and direct efficacy data, as noted above, is lacking. Therefore, it is important that participants accessing resources understand the limitations of knowledge regarding PEP, including almost certain absence of 100% protection, even given stringent entry criteria.

All subjects will be required to sign a one-time consent for documenting understanding of PEP procedures, risks to self and intimate contacts, course of treatment including a behavioral risk-reduction component and adherence counseling activities, as described in the informed consent and protocol.

10. Experts in HIV Clinical Care

Numerous references are made to conditions for invoking opinion or consultation with experts in HIV clinical care, including:

- A source who is known or suspected to be HIV positive with known or suspected viral resistance
- Incidental finding of HIV-positivity on rapid screening on initial intake
- Signs or symptoms consistent with PHI (Section 6.4, Table 1)
- Toxicity or intolerance to treatment medications beyond algorithms described in the protocol, or in the event of severe toxicity requiring discontinuation of any regimen
- Unclear provoking agent of toxicity with unclear optimal next treatment decision
- Any situation of PEP in pregnancy

An HIV Clinical Care Expert will be available on a rotating on-call system for the P-QUAD program, to be accessed by program staff ONLY, 24 hours per day.

11. Funding

Los Angeles County Office of AIDS Programs and Policy

Drug Supply from:

Gilead Sciences
Foster City, California

Glaxo SmithKline
Research Triangle Park, North Carolina

Abbott Pharmaceuticals
Abbott Park, Illinois

Merck, Incorporated
Whitehouse Station, Pennsylvania

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