Formulating the Future Research Agenda for Postexposure Prophylaxis for HIV: Methodological Challenges and Potential Approaches

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Background. During a World Health Organization–convened Guideline Development Group meeting, recommendations for postexposure prophylaxis (PEP) for human immunodeficiency virus were made and research gaps identified.

Methods. We used the PEP clinical management pathway and the Grading of Evidence, Assessment, Development and Evaluation (GRADE) system as a framework to formulate future research questions, describe the most feasible study design, and identify potential biases.

Results. Three key study design formats were identified to address 12 research questions: (1) survey- and interview-driven research to identify barriers to access to PEP and related clinical care; (2) establishment of a global PEP registry to generate data to inform the choice of an optimal PEP drug regimen, record drug toxicities arising from specific PEP regimens, and track follow-up and linkage to care (including transition from PEP to preexposure prophylaxis); and (3) randomized controlled trials to determine the optimal adherence promotion strategies necessary for successful outcomes following PEP.

Conclusions. Positioning key clinical and programmatic research questions within the GRADE framework facilitates the formulation of an evidence-based research agenda and future revisions of guidelines.

Keywords. HIV; postexposure prophylaxis; research agenda; guidelines; GRADE.

In June 2014, the World Health Organization (WHO) revised the global evidence-based recommendations for the use of antiretrovirals for postexposure prophylaxis (PEP) to prevent human immunodeficiency virus (HIV) transmission in the light of current evidence [1]. The process was supported by a Guideline Development Group (GDG) of experts in the field who reviewed evidence from key systematic reviews to formulate new recommendations for drug choice, prescribing methods, and clinical management. An essential component of any systematic review, as well as guideline development, is the identification of key research gaps. In this article, we present potential approaches for the conduct of future HIV PEP research to overcome feasibility or practical challenges that may arise. We demonstrate how the Grading of Evidence, Assessment, Development and Evaluation (GRADE) system can be used effectively as a conceptual framework and tool beyond the determination and qualification of recommendations to identify future research priorities and methodological challenges for research.

GRADE System

WHO has adopted the GRADE system for the development of global clinical, programmatic, and public health guideline recommendations [2]. The GRADE system

allows for the explicit use of factors that can increase or decrease the quality of the evidence from a starting point determined by study design [3]. In addition to appraising the quality of evidence, the GRADE approach includes an assessment of potential benefits and harms, resource utilization, and user values and preferences. The GDG considers these elements together to determine the direction and strength of a recommendation.

METHODS

Each recommendation made by the WHO HIV PEP GDG (see Acknowledgements) was driven by an a priori clinical or programmatic question that was identified along the clinical management pathway for HIV PEP (Figure 1). A systematic review conducted for each question and GRADE Evidence Profile tables summarizing the overall quality of evidence from each systematic review were presented to the GDG. The GDG subsequently formulated a recommendation and determined the strength of each recommendation.

For each stage on the clinical management pathway, we tabulated the following: (1) the clinical or programmatic question; (2) the recommendation formulated by the GDG or a record that no recommendation was made; (3) the strength of each recommendation where applicable; (4) the quality of evidence underpinning the recommendation; (5) the most appropriate study design to answer the research question; (6) conceptualization of a pragmatic alternative study design if the ideal design was not feasible; and (7) consideration of the methodological challenges of the study design with the potential bias(es) identified.

In addition to making recommendations, the GDG experts also considered the clinical management pathway of HIV PEP and additional associated research gaps.

RESULTS

Table 1 provides an overview of future PEP research priorities and the study design(s) considered most feasible to answer each clinical or programmatic question. Overall, 3 key study design formats were identified to address 12 questions: (1) survey- and interview-driven research to identify barriers to access to PEP and related clinical care; (2) establishment of a global PEP registry to generate data to inform the choice of an optimal PEP drug regimen, to record drug toxicities arising from specific PEP regimens, and to track follow-up and linkage to care (including transition from PEP to preexposure prophylaxis [PrEP]); and (3) randomized controlled trials (RCTs) to determine the optimal adherence promotion strategies necessary for successful outcomes following PEP.

DISCUSSION

We applied the GRADE framework to enhance the identification and description of the most appropriate and feasible research required to strengthen the evidence base for current and future PEP recommendations. By taking into account both quality of the available evidence and the strength of current recommendations, we were able to clearly identify research gaps. Where recommendations had not been made, expert knowledge of the PEP clinical management pathway allowed the GDG to formulate key research questions and identify the necessary study design. The generation of new data to inform PEP guidelines is challenged by the specific circumstances of the clinical encounter. HIV transmission is a low-probability event (because of biological and behavioral cofactors) and a high-consequence outcome for the affected individual [4]. Hence, PEP administration is often done in emergency settings, with high levels of anxiety expressed by those who present for PEP. Yet, because of the low average per-contact HIV risk, people who do not take PEP, or who initiate treatment but are nonadherent, and who only sustain a discrete high-risk exposure are not likely to become HIV infected. The relative inefficiency of HIV transmission for the majority of exposures that require PEP limits the ability to conduct randomized trials of different PEP regimens, durations of treatment, counseling protocols, and postregimen follow-up protocols.

Future Research Priorities
Qualitative Research
Identification of barriers to accessing care is a key challenge in ensuring timely and appropriate prescription of PEP. Expert members of the GDG shared anecdotal reports of settings
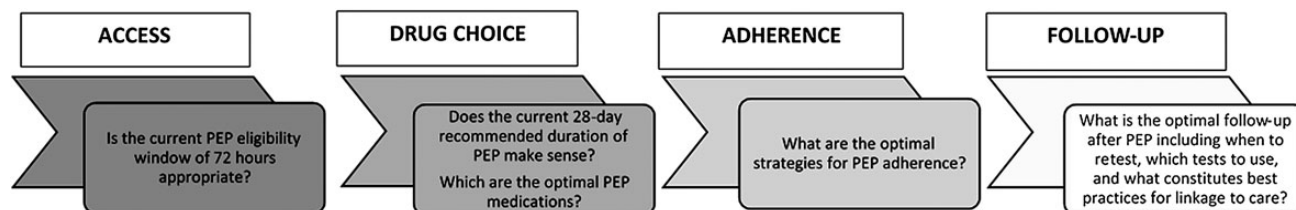

Figure 1. Clinical management pathway of postexposure prophylaxis (PEP) and key clinical and programmatic questions.

Table 1. Future Research Priorities Categorized According to the Postexposure Prophylaxis Clinical Management Pathway and Identified Using the GRADE Framework

Clinical or Programmatic Question	Current WHO Recommendation	Strength of Recommendation	Quality of Evidence	Ideal Study Design(s)	Feasibility and Practical Constraints	Alternative Study Design	Methodological Issues Arising
Access							
What are provider attitudes and knowledge regarding PEP and PEP prescribing practices?	No recommendation—not included as a question in initial guideline formulation	Not applicable	Expert opinion	Ethnographic observational study of point of care and audit of corresponding medical records, using diverse settings where PEP may be prescribed (eg, primary care clinics, emergency rooms, STD specialty clinics)	1. Time constraints within emergency settings 2. Access to medical records may be ethically challenging	Cross-sectional survey of providers regarding knowledge, attitudes, and practice of PEP	Selection bias: Those most likely to participate may be those providers who are already familiar with PEP. Generalizability: PEP is provided in diverse settings, and the global HIV epidemic affects different populations in different countries.
What barriers exist to accessing PEP?	No recommendation—not included as a question in initial guideline formulation	Not applicable	Expert opinion	Cross-sectional survey of PEP recipients in all settings	1. Potential difficulty obtaining informed consent in emergency settings 2. High anxiety of participants at access point to PEP may reduce levels of participation	Qualitative interviews with PEP recipients on completion of PEP course in specific settings. Future research may include methods to overcome barriers once these are identified.	Recall bias: Data collected after the point of access may limit the accuracy of participants' responses. PEP users who experience barriers and/ or poor treatment may be more likely to be lost to follow-up.
Timing and duration of the intervention							
Timing of PEP	Within 72 h (best practice)	Not applicable	Very low	RCT	Ethical	Adequately powered animal studies	Generalizability of animal data to humans; equipoise of providers
Duration of PEP	28 d (best practice)	Not applicable	Very low	RCT	Ethical	Adequately powered animal studies	Generalizability of animal data to humans; equipoise of providers
Drug choice							
What is the optimal number of drugs to prescribe for PEP?	A 2-ARV-drug regimen is effective, but 3 drugs are preferred.	Conditional	Low	RCTs of comparative effectiveness and safety between 2- and 3-drug regimens	An RCT would require a large sample size for adequate power to detect significant differences. HIV transmission is inefficient; PEP numbers at individual sites are low and occur in a wide range of settings, limiting the desired sample size and generalizability.	Cohort analysis following recipients receiving different regimens or Global PEP Registry	Confounding: The impact of additional exposure(s) to HIV transmission post–PEP regimen will be a key confounder in a cohort study. Provider familiarity with PEP, and site support for PEP, may confound interpretation of regimens.

Table 1 continued.

Clinical or Programmatic Question	Current WHO Recommendation	Strength of Recommendation	Quality of Evidence	Ideal Study Design(s)	Feasibility and Practical Constraints	Alternative Study Design	Methodological Issues Arising
What are the preferred drugs to use in the backbone PEP regimen in adults and adolescents?	TDF+3TC (or FTC) is recommended as the preferred backbone regimen for HIV PEP in adults and adolescents.	Strong	Low to moderate	RCTs of comparative effectiveness and safety between different ARV drug regimens	Rapidly evolving profile of recommended ARVs may result in within-trial regimen change. As above, an RCT would require high numbers for adequate power to detect significant difference.	Global PEP Registry	Confounding: impact of additional exposure to HIV post PEP regimen. Provider familiarity with PEP, and site support for PEP, may confound interpretation of regimens.
What is the preferred third drug(s) to use for PEP in adults and adolescents?	LPV/r or ATV/r is suggested as preferred third drug for HIV PEP in adults and adolescents. Where available, the following alternatives can be considered: DRV/r, RAL, EFV.	Conditional	Very low	As above	As above	As above	As above
What are the preferred drugs to use in the backbone regimen for PEP for children aged ≤10 y?	ZDV+3TC is recommended as the preferred backbone for HIV PEP in children aged ≤10 y. ABC+3TC or TDF+3TC (or FTC) can be considered as alternative regimens.	Strong	Low	As above	As above	As above	As above
What is the preferred third drug for PEP for children aged ≤10 y?	LPV/r is recommended as the preferred third drug for HIV PEP in children aged ≤10 y. ATV/r, RAL, NVP (if aged <3), and EFV or DRV/r (if 3 y and older) can be considered as alternatives.	Conditional	Very low	As above	As above	As above	As above
Adherence							
Should 28 d (full) vs starter packs be used for prescribing PEP?	A full 28-d prescription of ARVs should be provided for HIV PEP following initial risk assessment.	Strong	Very low	No further research needed. An RCT is unlikely to change the strength of the recommendation, which was based on feasibility and practical implementation considerations.		A Global PEP Registry will allow identification of those settings where starter packs are still provided. This will be for monitoring and evaluation purposes and not research.	Confounding: Providers and sites that use starter packs may have other characteristics that could affect outcomes (eg, more or less experience, supportive environment).

Table 1 continued.

Clinical or Programmatic Question	Current WHO Recommendation	Strength of Recommendation	Quality of Evidence	Ideal Study Design(s)	Feasibility and Practical Constraints	Alternative Study Design	Methodological Issues Arising
What types of adherence strategies should be offered during PEP?	Enhanced adherence counseling is suggested for all individuals initiating HIV PEP.	Conditional[a]	Moderate	An RCT comparing specific adherence strategies in the context of PEP	Sample size would be extremely large, as providing no adherence support would likely be considered unethical, resulting in 2 active arms.	Documentation of outcomes from single or multisite PEP adherence interventions with comparison to historical controls may provide guidance for replication in other settings; Global PEP Registry would require data fields to describe diverse interventions.	Confounding: May be challenging to randomize by patients within sites, as the same providers would be required to deliver 2 different PEP adherence interventions. Provider and site characteristics would make comparison of interventions randomized by site difficult.
Follow-up and linkage to care							
What is the optimal testing and linkage to care package for PEP?	No—not included as a question in initial guideline formulation	Not applicable	Expert opinion	An RCT comparing different strategies for post-PEP testing	Sample size would be extremely large, as providing no follow-up testing would be considered unethical, resulting in 2 active arms.	Documentation of outcomes from single or multisite post-PEP testing algorithms with comparison to historical controls may provide guidance for replication in other settings; Global PEP Registry would require data fields to describe diverse interventions.	Confounding: Would be challenging to randomize by patients within sites, as the same providers would be required to use 2 different PEP testing algorithms. Provider and site characteristics would make comparison of testing algorithms randomized by site difficult.
When should PEP be transitioned to PrEP?	No—not included as a question in initial guideline formulation	Not applicable	Expert opinion	An RCT comparing different approaches to assess patients for PEP, and to triage them to PrEP	Sample size would be extremely large; not assessing any PEP patients for PrEP could be considered unethical, resulting in 2 active arms.	Documentation of outcomes from single or multiple sites' PEP-PrEP triage programs, with comparison to historical controls, may provide guidance for replication in other settings; Global PEP Registry would require data fields to describe diverse algorithms and programs for PEP-PrEP transition.	Confounding: Would be challenging to randomize by patients within sites, as the decision to discuss PrEP would be based on numerous patient-specific issues (eg, likelihood of subsequent repetitive HIV risk, adherence to PEP regimen, patient interest in PrEP), making comparison of triage algorithms difficult.

Abbreviations: 3TC, lamivudine; ABC, abacavir; ARV, antiretroviral; ATV/r, ritonavir-boosted atazanavir; DRV/r, ritonavir-boosted darunavir; EFV, efavirenz; FTC, emtricitabine; HIV, human immunodeficiency virus; LPV/r, ritonavir-boosted lopinavir; NVP, nevirapine; PEP, postexposure prophylaxis; PrEP, preexposure prophylaxis; RAL, raltegravir; RCT, randomized controlled trial; STD, sexually transmitted disease; TDF, tenofovir disoproxil fumarate; WHO, World Health Organization; ZDV, zidovudine.

[a] This recommendation appears in the WHO 2013 Antiretroviral Therapy Consolidated Guidelines and was adopted for the PEP guidelines.

where healthcare workers were reluctant to prescribe PEP and concluded that there was a wide-scale lack of knowledge of the benefits of PEP among healthcare workers. Identification of the knowledge, attitudes, and prescription practices of PEP providers with associated documentation of the care experiences of PEP recipients would require survey- and interview-driven research. Formulation of appropriate comparative questions and evidence-based recommendations regarding the factors required to optimize delivery and receipt of PEP in the future would only be possible once such baseline data were available. Social desirability bias might limit the ability to be confident that provider self-reports would mirror clinical practice.

Global Registry

Ideally, evidence to inform guidelines of interventions should be based on data obtained from RCTs. Yet alternative study designs must be considered when there are ethical, statistical, and practical challenges to the feasibility of conducting an RCT as outlined in Table 1. Given that PEP is provided across many and varied settings and PEP provision and uptake is generally low, the GDG recommended that a global PEP registry be established to standardize data reporting, to record toxicities due to PEP, to help inform future PEP drug regimen choice for both adults and children, and to potentially also provide information to track follow-up and linkage to care. Registries have already been established for other HIV research questions for which RCTs are not possible [5], notably drug safety in pregnancy, and data generated from such registries have directly informed WHO guidance [6].

RCTs of Adherence Strategies

Alternative methods of adherence support were considered in the WHO 2013 antiretroviral therapy guidelines [7], and several of these may be suitable to PEP (such as peer support, alarms, text messaging, phone calls, and calendars), but the effectiveness of these interventions for HIV-uninfected individuals in the context of PEP has not been evaluated. At the same time, it is recognized that adherence research is notoriously difficult owing to the small event-rate differences, limiting the ability of any single trial to show significant differences [8]. Future efforts to identify interventions to improve adherence to PEP should therefore be informed by HIV treatment and other medication adherence research and lessons learned from similar interventions, including, for example, PrEP [9], oral contraception, and the management of hypertension, and treatment of latent tuberculosis infection.

The Special Case of PEP to PrEP

When PEP was first recommended for the prevention of occupational HIV exposures [10], the presumption was that exposures were not intentional and would be infrequent. The recognition of settings of sexual assault, condom failure, and discovery that a partner was HIV infected after exposure led to the development of recommendations for the use of comparable regimens for nonoccupational PEP [11]. Subsequent studies found that some nonoccupational PEP users presented more than once, and a subset became recurrent users [12]. With the subsequent determination that the preexposure use of antiretrovirals could significantly decrease HIV incidence (PrEP) [13], it is clear that a subset of people presenting for PEP could benefit from PrEP [14]. Because many PEP users may not be at recurrent risk, new research studies are needed to assist front-line PEP providers to efficiently determine which PEP users could benefit by transitioning to PrEP. Many of the nuances of optimal management are discussed in the article by Jain et al in this supplement [15], but further research is warranted, given the newness of PrEP and the lack of a sufficient evidence base to suggest best practices.

Strengths and Limitations of the GRADE Approach to Prioritize Research

The structure and direction of the GRADE framework provided a useful starting point for the GDG discussions of future research priorities. Low-quality evidence is the first and most powerful indicator of the need for future and/or more robust research to underpin recommendations. The strength of a recommendation can also be informative, with conditional recommendations generally indicating the need for further research compared with recommendations rated as strong. However, several WHO guidelines have included strong recommendations based on low-quality evidence [16]. Three of the recommendations in these PEP guidelines are strong in the absence of high-quality evidence. These include the recommendation for a full 28-day prescription of antiretrovirals for HIV PEP following initial risk assessment (rated as very low quality); the recommendation for zidovudine (ZDV) plus lamivudine (3TC) as the preferred backbone for HIV PEP in children aged ≤10 years and that abacavir plus 3TC or tenofovir disoproxil fumarate (TDF) plus 3TC (or emtricitabine [FTC]) can be considered as alternative regimens (rated as low quality); and the recommendation that TDF plus 3TC (or FTC) is the preferred backbone regimen for HIV PEP in adults and adolescents (rated as low to moderate quality). This apparent contradiction between strength and ratings reflects that factors such as values, preferences, and resource utilization can drive the strength of the recommendation in addition to the quality of evidence.

Several clinical and programmatic questions were identified directly from the PEP clinical management pathway based on expert opinion gathered together in the GDG. We believe that positioning these questions within the GRADE framework will facilitate future revisions of the PEP guidelines given that the key questions in association with the required study design are well articulated, and can be addressed as new data emerge.

Notes

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