

Annex 2: Systematic review protocol

Safety and efficacy of antiretroviral drugs for post-exposure prophylaxis: a systematic review

1. INTRODUCTION

Post-exposure prophylaxis (PEP) involves the provision of antiretroviral drugs following exposure to the human immunodeficiency virus in order to inhibit virus replication and thereby prevent the establishment of chronic HIV infection.

PEP is recommended by various national and international guidelines for occupational, accidental and sexual exposure. The number and type of antiretroviral drugs that are recommended may differ, with certain guidelines recommending two drugs for most HIV exposures, with a three-drug regimen advised for exposures that pose an increased risk of HIV transmission (eg exposure to large volumes of blood, deep injuries, and blood containing known high levels of HIV). However, policy and practice varies and the evidence base supporting the various recommendations is uncertain.

This systematic review aims to assess the safety and efficacy of different PEP regimens to inform future WHO guidance.

2. METHODS

2.1. Search strategy

An initial search strategy has been developed, and the list of titles was then cross-checked against existing PEP systematic reviews. Missing studies were then reviewed to identify additional terms to develop the final search strategy, which is detailed below.

1.	HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tiab] OR hiv-1*[tiab] OR hiv-2*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect*[tiab] OR human immunodeficiency virus[tiab] OR human immunodeficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR human immune-deficiency virus[tiab] OR ((human immun*[tiab]) AND (deficiency virus[tiab])) OR acquired immunodeficiency syndrome[tiab] OR acquired immunodeficiency syndrome[tiab] OR acquired immuno-deficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun*[tiab]) AND (deficiency syndrome[tiab])) OR "sexually transmitted diseases, Viral"[MeSH:NoExp]
2.	Post exposure prophylaxis[tiab] OR postexposure prophylaxis[tiab] OR post-exposure prophylaxis[tiab] OR PEP[tiab] OR anti-infection prophylaxis[tiab] OR post-exposure HIV prophylaxis[tiab] OR chemoprevention[tiab] OR exposure prophylaxis
3.	1 AND 2

2.2. Databases

The following databases will be searched from inception to 1 December 2013.

- Medline via Pubmed
- Embase
- Cochrane Database of Systematic Reviews
- Lilacs

In addition, all Conferences of the International AIDS Society will be searched from 2010 onwards to identify studies that have been completed but not yet published as full text.

2.3. Restrictions

No date, language, or geographical exclusions will be applied.

2.4. Types of studies

- Randomized-controlled trials
- Prospective cohorts
- Case series >10 patients will be included

In the absence of sufficient data from the above study designs, retrospective cohorts will also be included.

2.5. Types of participants

Inclusions

- Adults and children exposed to HIV and provided with a course of PEP irrespective of exposure

Exclusions

- PEP given as monotherapy
- Infants exposed *in utero* and provided with PMTCT
- Animal studies

2.6. Types of outcomes

The following outcomes will be reported:

- Number initiating PEP among those eligible (cohorts only)
- Treatment completion: defined as completing the full (4 week) course of treatment
- Safety, defined as frequency of adverse events
- PEP discontinuations due to adverse events
- Adherence to treatment: adherence measure as defined by the studies
- Efficacy, defined as the absence of HIV infection following PEP

3.0. Risk of bias

Risk of bias will be assessed using appropriate tools for randomized trials and observational studies, adapted according to the final list of inclusions.

The risk of bias items assessed were as follows:

3.1. *Randomized trials*

- Method of randomization described
- Method of allocation concealment described
- Reasons for discontinuation provided
- No patient selection with respect to study inclusions
- No patient selection with respect to outcome reporting

3.2. *Observational studies*

- PEP refusal <20%
- Objective adherence assessment
- Reasons for discontinuation provided
- Side-effects reported
- Clear inclusion and exclusion criteria
- No patient selection with respect to study inclusions
- No patient selection with respect to outcome reporting

4.0. **Quantitative synthesis**

Descriptive statistics will be used to compare the number of studies published over time. Point estimates and 95% confidence intervals will be calculated for the proportion of individuals reaching each step in the cascade of care from eligibility determination to attendance of follow up visit. In instances where PEP was discontinued due to confirmation of prior HIV-positivity or HIV-negative exposure status, these cases will be excluded from the denominator for assessing PEP completion rates and reported separately. Data will be pooled using the DerSimonian-Laird random-effects method,¹ with proportions transformed prior to pooling using the Freeman-Tukey double arcsine transformation² and then back-transformed to the original scale.³ We will calculate the τ^2 statistic using DerSimonian and Laird method of moments estimator to assess between-study heterogeneity.⁴

Pre-planned subgroup analyses will undertaken to determine the potential influence of the following covariates:

- exposure type
- age
- regimen type (2 vs 3 drugs); protease inhibitors
- regimen prescribing practice (full course vs starter pack
- study design
- level of economic development (as defined by the World Bank <http://data.worldbank.org/about/country-classifications>).

All P values will be reported as two-sided and P<.05 considered significant. All analyses were conducted using Stata version 12.0 (StataCorp, College Station, Tex).

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Supplementary Table 1: Characteristics of included studies

Study	Year	Design	Exposure	Population	Country	Number of ARVs	Starterpack (type)
Abrahams ¹	2010	RCT	Sexual assault	All	South Africa	2	Yes (3 days)
Aggarwal ²	2012	Retrospective	Occupational	Adults	India	2	Yes (3 days)
Armishaw ³	2011	Prospective	Non-occupational	Adults	Australia	2	No
Babl ⁴	2000	Retrospective	Sexual assault	Adolescents	USA	3	No
Bentz ⁵	2010	RCT	Non-occupational	Adults	France	3	No
Bernasconi ⁶	2001	Prospective	Non-occupational	All	Switzerland	3	NS
Bogoch ⁷	2014	Prospective	Non-occupational and occupational	Adults	USA	3	Yes (3 days)
Braitstein ⁸	2002	Prospective	Non-occupational and occupational	NS	Canada	2	Yes (5 days)
Burty ⁹	2008	Prospective	Non-occupational and occupational	Adults	France	3	Yes (3 days)
Burty ¹⁰	2010	Prospective	Non-occupational and occupational	Adults	France	3	Yes (3 days)
Carries ¹¹	2007	Retrospective	Sexual assault	All	South Africa	2	Yes (3 days)
Carrieri ¹²	2006	Retrospective	Sexual assault	Adults	France	3	NS
Chan ¹³	2013	Retrospective	Non-occupational	Adults	Canada	3	Yes (5 days)
Collings ¹⁴	2008	Prospective	Sexual assault	Children	South Africa	2	Yes (5 days)
Day ¹⁵	2006	Retrospective	Non-occupational	Adults	UK	3	Yes (3 days)
De Waal ¹⁶	2005	Prospective	Non-occupational	Children	South Africa	2	No
Diaz-Brito ¹⁷	2012	RCT	Non-occupational and occupational	Adults	Spain	3	Yes (3 days)
Diniz ¹⁸	2007	Prospective	Sexual assault	All	Brazil	NS	NS
Ehui ¹⁹	2010	Retrospective	Sexual assault	Adolescents	Cote d'Ivoire	3	Yes (3 days)
Ellis ²⁰	2005	Prospective	Sexual assault	Children	Malawi	2	No
Fatkenheuer ²¹	2014	RCT	Non-occupational and occupational	Adults	Germany	3	NS
Garb ²²	2002	Prospective	Occupational	Adults	USA	2	Yes (4 days)
Garcia ²³	2005	Prospective	Sexual assault	Adults	Brazil	2	No
Gounden ²⁴	2000	Retrospective	Occupational	Adults	South Africa	2	NS
Greub ²⁵	2002	Prospective	Non-occupational	Adults	Switzerland	3	NS
Griffith ²⁶	2010	Retrospective	Sexual assault	Adults and adolescents	USA	3	NS
Grime ²⁷	2001	Retrospective	Occupational	Adults	UK	3	NS
Gulholm ²⁸	2013	Retrospective	Non-occupational	Adults	Australia	3	Yes (6 days)
Gupta ²⁹	2008	Prospective	Occupational	Adults	India	NS	Yes (7 days)
Hachey ³⁰	2005	Retrospective	Sexual assault	Children	South Africa	NS	NS
Hiransuthikul ³¹	2007	Retrospective	Occupational	Adults	Thailand	2	NS
Izulla ³²	2013	Prospective	Non-occupational	Adults	Kenya	2	Yes (10 days)
Kahn ³³	2001	Prospective	Non-occupational	Adolescents and adults	USA	NS	No
Kiertiburanakul ³⁴	2005	Retrospective	Occupational	Adults	Thailand	2	NS
Kim ³⁵	2006	Prospective	Sexual assault	All	South Africa	2	NS
Lacombe ³⁶	2006	Prospective	Non-occupational	Adults	France	NS	No
Landovitz ³⁷	2012	Prospective	Non-occupational	Adults	USA	2	No
Landovitz ³⁸	2010	Prospective	Non-occupational	Adults	USA	2	No
Laporte ³⁹	2002	Retrospective	Non-occupational	All	France	NS	NS
Limb ⁴⁰	2002	Retrospective	Sexual assault	NS	UK	3	No
Linden ⁴¹	2005	Retrospective	Sexual assault	Adults	USA	2	Yes (3 days)
Loufty ⁴²	2008	Prospective	Sexual assault	All	Canada	3	Yes (3 days)
Lunding ⁴³	2010	Retrospective	Non-occupational	Adolescents and adults	Denmark	3	NS
Luque ⁴⁴	2007	Retrospective	Non-occupational and occupational	Adults	USA	3	NS

Manavani ⁴⁵	2004	Retrospective	Non-occupational and occupational	NS	UK	3	Yes (3 days)
Mashoto ⁴⁶	2013	Retrospective	Occupational	Adults	Tanzania	NS	NS
Mathewos ⁴⁷	2013	Retrospective	Occupational	Adults	Ethiopia	NS	NS
Mayer ⁴⁸	2008	Prospective	Non-occupational	Adults	USA	2	NS
Mayer ⁴⁹	2012	Prospective	Non-occupational	Adults	USA	3	NS
McAllister ⁵⁰	2013	Prospective	Non-occupational	Adults	Australia	NS	No
McCarty ⁵¹	2011	Retrospective	Non-occupational	Adults	UK	3	NS
Minas ⁵²	2012	Retrospective	Non-occupational	Adolescents and adults	Australia	NS	NS
Morgan ⁵³	2014	Retrospective	Sexual assault	Adults	UK	3	Yes (3 days)
Neu ⁵⁴	2007	Prospective	Sexual assault	Adolecents	USA	2	Yes (NS)
Okulicz ⁵⁵	2012	Retrospective	Occupational	Adults	Afghanistan	2	NS
Olatunya ⁵⁶	2014	Retrospective	Sexual assault	Children	Nigeria	2	NS
Olowookere ⁵⁷	2010	Retrospective	Non-occupational and occupational	All	Nigeria	3	NS
Olshen ⁵⁸ *	2006	Retrospective	Sexual assault	Adolescents	USA	2	NS
Pai ⁵⁹	2013	Prospective	Non-occupational	Adults	Canada	3	Yes (7 days)
Papenburg ⁶⁰	2008	Prospective	Non-occupational	Children	Canada	2	NS
Parkin ⁶¹	2000	Retrospective	Occupational	Adults	UK	3	NS
Patel ⁶²	2002	Retrospective	Occupational	Adults	UK	NS	NS
Poynten ⁶³	2007	Prospective	Non-occupational	Adults	Australia	3	NS
Puro ⁶⁴	2003	Retrospective	Occupational	Adults	Italy	3	NS
Rabaud ⁶⁵	2001	Prospective	Occupational	Adults	France	3	No
Rabaud ⁶⁶	2005	Prospective	Non-occupational and occupational	Adults	France	3	Yes (2 days)
Reeves ⁶⁷	2004	Retrospective	Sexual assault	Adults	UK	NS	Yes (NS)
Rey ⁶⁸	2004	Retrospective	Non-occupational and occupational	Adolescents and adults	France	3	No
Roedling ⁶⁹	2008	Retrospective	Non-occupational	Adults	UK	3	NS
Roland ⁷⁰	2011	RCT	Non-occupational	Adults	USA	2	Yes (10 days)
Roland ⁷¹	2012	Prospective	Sexual assault	Adolescents and adults	South Africa	2	Yes (7 days)
Schechter ⁷²	2004	Prospective	Non-occupational	Adults	Brazil	2	Yes (4 days)
Schremmer ⁷³	2005	Retrospective	Sexual assault	Children and adolescents	USA	2	Yes (14 days)
Selenic ⁷⁴	2013	Retrospective	Occupational	Adults	Zambia	NS	NS
Sepkowitz ⁷⁵	1998	Retrospective	Occupational	Adults	USA	3	NS
Shevkani ⁷⁶	2011	Prospective	Occupational	Adults	India	3	NS
Shoptaw ⁷⁷	2008	Prospective	Non-occupational	Adults	USA	2	Yes (NS)
Siika ⁷⁸	2009	Retrospective	Sexual assault	Adults	Kenya	3	NS
Sonder ⁷⁹	2007	Prospective	Non-occupational	Adolescents and adults	Netherlands	3	Yes (NS)
Sonder ⁸⁰	2010	Prospective	Non-occupational	Adolescents and adults	Netherlands	3	Yes (NS)
Speight ⁸¹	2006	Prospective	Sexual assault	Adults and children	Kenya	2	NS
Swotinsky ⁸²	1998	Prospective	Occupational	Adults	USA	NS	NS
Tan ⁸³	2014	Prospective	Non-occupational and occupational	Adults	Canada	3	NS
Tetteh ⁸⁴	2013	Retrospective	Occupational	Adults	Ghana	2	Yes (3 days)
Thomas ⁸⁵	2006	Prospective	Non-occupational	Children	UK	3	Yes (3 days)
Tissot ⁸⁶	2010	Retrospective	Non-occupational	Adolescents and adults	Switzerland	3	No
Tosini ⁸⁷	2010	Prospective	Non-occupational and occupational	Adults	France	3	Yes (3 days)
de la Tribonniere ⁸⁸	1998	Retrospective	Occupational	Adults	France	3	NS
Van der Ende ⁸⁹	2002	Prospective	Non-occupational and occupational	Adults	Netherlands	3	NS

Wang ⁹⁰	2000	Prospective	Occupational	Adults	USA	3	NS
Whitehead ⁹¹	2010	Retrospective	Non-occupational and occupational	Adolescents and adults	UK	3	Yes (3 days)
Wiebe ⁹²	2000	Prospective	Sexual assault	Adolescents and adults	Canada	2	Yes (5 days)
Winston ⁹³	2005	Prospective	Non-occupational	Adults	Australia	NS	No
Wong ⁹⁴	2010	Retrospective	Non-occupational and occupational	Adolescents and adults	Canada	2	Yes (5 days)
van der Maaten ⁹⁵	2010	Retrospective	Occupational	Adults	Malawi	2	Yes (NS)
van der Maaten ⁹⁶	2011	Retrospective	Non-occupational	NS	UK	3	NS

* This paper reported data from 2 different studies. NS, not stated

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Supplementary Table 2: reported seroconversions

Study	Exposure	Seroconverted (N=37)	Follow up	Reason provided
Carries	Sexual assault	1	1.5 months	Client filled only the first 1-week prescription; subsequent exposure to HIV unknown
Roland	Sexual assault	4	6 months	2 probable PEP failures (1 with excellent reported adherence and 1 with incomplete adherence. 2 probable ongoing exposures
Amrishaw	Non-occupational	6	3 months	3 identified at subsequent baseline PEP presentation 3 reported significant risk exposures either before or after receipt of NPEP
Chan	Non-occupational	2	3 months	Ongoing potential exposure
Gulholm	Non-occupational	2	6 months	Ongoing high-risk behaviours
Landovitz	Non-occupational	1	3 months	Medication non-adherence and multiple subsequent sexual exposures
Lundig	Non-occupational	1	3 months	Probably due to repeated exposures during and after completion of PEP
Roland	Non-occupational	13	Not stated	12 month cumulative incidence of HIV seroconversion
Schechter	Non-occupational	1	Not stated	PEP failure
Sonder	Non-occupational	5	3 months	Seroconverted despite good adherence; none resistant to PEP regimen. Likely caused by ongoing exposure
Van der Maarten	Non-occupational	1	Not stated	First test was done after starting PEP and timing of HIV acquisition uncertain