

A protocol for systematic review on global diversity of human immunodeficiency virus-1 subtypes

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Abstract

Background: Human Immunodeficiency Virus (HIV)-1 subtypes are heterogeneously distributed around the world. Recent works on near full-length genome sequencing of HIV-1 shows increasing events of different recombinant variants and subtype C viruses. The active change in HIV-1 subtype distribution patterns initiate global challenges for diagnosis, treatment and antiretroviral (ARV) drug design.

Objectives: Present study has been initiated to provide a summary of the current data on the HIV-1 subtype diversity and distribution by region.

Methods: The data will be extracted through data extraction form as per Population, Intervention, Comparison, Outcomes and Study (PICOS) framework. Risk of bias and quality assessment will be performed with the help of Egger's test and modified Newcastle - Ottawa Quality Assessment Scale respectively. The protocol registration number was International Prospective Register for Systematic Reviews (PROSPERO) number CRD42023400199.

Results: The pattern of HIV-1 subtypes and Circulating Recombinant Form (CRF)/Unique Recombinant Form (URF) along with their geographical distribution around the world.

Conclusion: The future systematic review, which will be generated from the present protocol, may provide evidence of the diversity of HIV-1 subtypes around the world. The present protocol might be handy to conduct a systemic review (and meta-analysis, if possible) on the global diversity of HIV-1 subtypes.

Key words: Diversity; Human immunodeficiency virus-1; Human immunodeficiency virus-2; Subtype.

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INTRODUCTION

Human immunodeficiency virus (HIV)-1 and HIV-2 are genetically diverse lentivirus^{1,2} that evolved through cross-species transmissions from non-human primates. Moreover, mutation rate is similar from new-to-old age distribution of non-human primates, resulting a zoonotic transmission. HIV-1 is divided into four groups such as M (Major), O (Outlier), N (Non-major, Non-outlier), and newly described P (Putative).² Comprehensive outbreak of virus is marked by well-defined geographical distribution. Subtype-B became prevalent in Europe and United States of America (USA).³ Other subtype and inter-subtype recombinant varieties evolved mainly in West Central Africa.⁴ Group-M with nine subtypes (A-D, F-H, J, K) dominates global HIV distribution, compared to N, O, and P. Moreover, circulating recombinant forms (CRFs) are HIV-1 genomes that share same recombination breakpoints (BPs) between same parental and found in at least three non-epidemiologically-related individuals. If CRF requirements not fulfilled, it is unique recombinant form (URF).

Molecular diversity of HIV-1 poses significant task for antiretroviral (ARV) drug design, with limited available approaches. To comprehend biological consequences of HIV-1 inter-subtype diversity,⁵⁻⁹ molecular differences in functional genes to phenotype and serology, specifically subtypes-B and -C are linked. Diverse autologous humoral responses that differ in gp120 targets and cross-reactive extent, particularly in V3 region are associated.¹⁰⁻¹⁴ Different subtypes variations in different topography (B and C), also depict host population variations from which viruses evolved, epidemic patterns, route of infection, etc.¹⁵ Future systematic review (SR) will find subtype-specific differences in functional gene and serology to incorporate into ARV.¹⁶⁻¹⁸ There is little approach to study HIV-1 subtypes diversity through SR and meta-analysis (MA), which is initiated here, with SR protocol preparation on HIV-1 subtypes around world.

Objectives are to synthesise evidence on pattern and diversity of HIV-1 subtype and CRF/URF through SR (and MA) on existing prevalence (pooled prevalence in MA) and global distribution of HIV-1 subtype and CRF/URF diversity.

METHODOLOGY

A study protocol has been developed after following Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.¹⁹ The protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO),²⁰ with the registration number CRD42023400199.²¹

REVIEW QUESTIONS

1. What is the pattern of HIV-1 subtypes and CRF/URF around the world?
2. What is the geographical distribution of HIV-1 subtypes and CRF/URF around the world?

Inclusion Criteria: Any article published in peer-reviewed journals, and any reports published by the government and competent non-governmental agencies (NGOs) as grey literature during the accepted timeline (2017 January to 2022 December). The data will be extracted through data extraction form as per PICOS (Population, intervention, comparison, outcome, and study design) framework.

Population: People living with HIV-1.

Intervention: Not relevant to this review.

Comparison group: Not relevant to this review.

Outcome: The pattern of HIV-1 subtypes and CRF/URF along with their geographical distribution around the world.

Study design: Data will be extracted through a previously prepared data extraction²² form which includes different levels of data accumulation to obtain a general picture of diversity patterns of HIV-1 subtypes among people living with HIV-1 among the general and key populations belonging to different geographical regions in the world, from previously published articles, divided into cross-sectional or baseline studies or cohort studies, and different reports published by different agencies (international, provincial government, and non-governmental organisation), regarding this topic. After completion of data extraction, data will be analysed and a cumulative report of the systematic review will be generated.

Exclusion criteria: Non-peer-reviewed articles will only be accepted after quality assessment; Any article that does not contain data on HIV-1 subtypes will be excluded; Articles published not within the accepted timeline will be excluded, and Commentaries and editorials, which are devoid of primary data will be excluded.

Search strategies and selection process

Electronics databases:

The following databases will be searched from 2017 January to 2022 December for published articles in the English language. The search will be updated before initiating a statistical analysis.

- a) Medical Literature Analysis and Retrieval System Online (MEDLINE)
- b) Cochrane Library
- c) PsycINFO
- d) ScienceDirect
- e) Scopus
- f) Excerpta Medica Database (Embase)
- g) Google Scholar
- h) Public MEDline (PubMed)

GREY LITERATURE:

An extensive search will be carried out through the different governmental and non-governmental reports relevant to the study. The studies from grey literature will be included after being checked through Axis Tool, a Quality assessment tool for grey literature.²³

SEARCH TERMS:

Search	Query	Results
#8	#1 AND #6 AND #7	1,074
#7	#2 OR #3 OR #4 OR #5	110,713
#6	world OR earth OR global	1,607,763
#5	(HIV-1 circulating recombinant form) OR (HIV-1 CRF) OR (HIV-1 unique recombinant form) OR (HIV-1 URF)	811
#4	HIV-1 OR (Human immunodeficiency virus type-1) OR HIV-2 OR (Human immunodeficiency virus type-2)	110,713
#3	(HIV-1 type-M) OR (HIV-1 type-Major) OR (HIV-1 type-O) OR (HIV-1 type-Outlier) OR (HIV-1 type-N) OR (non-Major type HIV-1) OR (HIV-1 type-O) OR (non-Outlier type HIV-1)	108,439
#2	(HIV-1 Subtype-A) OR (HIV-1 Subtype-B) OR (HIV-1 Subtype-C) OR (HIV-1 Subtype-D) OR (HIV-1 Subtype-F) OR (HIV-1 Subtype-G) OR (HIV-1 Subtype-H) OR (HIV-1 Subtype-J) OR (HIV-1 Subtype-K)	4,370
#1	diversity OR distribution OR (spatial distribution)	2,144,869

ADDITIONAL SEARCH STRATEGIES:

- a) Details of the diversity of HIV-1 subtypes around the world.
- b) Experts in the field will be contacted to ask if they know of any additional publications, which will not be identified by the search strategy.

De-duplication: Mendeley bibliographic software for reference management will be used²⁴ in the future Systematic Review. The following rules will be used to remove duplicate hits from the database:

- a) Compare the titles, or various combinations of authors, year, secondary title, volume, issue, and pages through the 'de-duplication';
- b) Visually compare the full records of suspected duplicates;
- c) Save duplicates in as separate database.

Selection of eligible studies: Titles and abstracts of articles selected through the search strategy will be

screened by two reviewers independently, applying the inclusion and exclusion criteria. Any article selected as being probably qualified will be taken for the full-text review. Where no abstract will be available electronically, and eligibility could not be judged from the title alone, the full text of the article will be retrieved and screened. The abstracts of articles identified through additional searches will be reviewed in the same manner as those identified through database searches. Data will be extracted by data extraction form. Moreover, formal ethical approval is not required as the present work is based on secondary data set.

Strategy for data synthesis: The data will be extracted from full-text published articles according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) with the help of Epi Info. (Ver. 6.0) generated modified data extraction form.²⁵

DATA EXTRACTION FORM

A Protocol for Systematic Review and Meta-analysis on Global Diversity of HIV-1 subtypes

SL. No.	Date:
Author/s Name	
Publication Year	
Region/ State	
Study Period	
Study Type	
Sampling method/s:	
Age/ Age group:	
Belongs to any risk group:	
Any Medical Exposure:	
Population	Naïve On ART

Sampling technique:				
Overall sample size:				
Prevalence of HIV-1:				
A	D	BC	AG	CRF03_AB
B	F	BF	URF	CRF01_AE
C	G	DF	CRF02_AG	CRF07_BC
Kit Details:				
Sequencing platform:				
Remarks:				
Signature:	<input type="text"/>	<input type="text"/>		
	Data extracted by	Checked by		

Assessment of the methodological quality: Prior to their inclusion in the final analysis, articles will first undergo evaluation based on their title, abstract, and complete content. Assessment will be performed with the help of a modified Newcastle - Ottawa Quality Assessment Scale.²⁶

Publication bias analysis: To evaluate publication bias Egger's²⁷ and Begg and Mazumdar's²⁸ assessments will be used along with the Funnel diagram.

Descriptive analysis: The estimation of the frequency of different of HIV-1 subtypes will be carried out around the world.

Strengths and limitations of the study: Like any other systematic review, the present work will also be restricted by the inclusiveness of the published articles and whether workers published their study in open

accessed and peer reviewed journals as well as available reports from various agencies. Moreover, future included articles that will be included as per the current protocol may have to contain surveys that accumulate biological data leaving an approach for further researches.

Expected outcomes: The pattern of HIV-1 subtypes and CRF/URF along with their geographical distribution around the world. As we know that World Health Organisation (WHO) divides the world into six WHO regions, for the purposes of reporting, analysis and administration. Here the global divisions/ regions of countries made by WHO (derived from World Health Statistics 2011) was used.

CONCLUSION

The future systematic review (and meta-analysis, if possible), which will be generated from the present protocol, may provide evidence of the diversity of HIV-1 subtypes around the world. The present protocol might be handy to conduct a systemic review on the global diversity of HIV-1 subtypes.

Conflict of interest: None.

Source(s) of support: None.

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