Annex I. Methodological quality appraisal and Grading of Studies included in the systematic review

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| First author: | Setting | Design | Quality level of a body of evidence \_GRADE | | | | |  | NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE | | |
| Limitations in the design & implementation | Indirectness Of Evidence | Unexplained heterogeneity | Imprecision of results | High probability of publication bias: | Grade | Selection | Comparability | Outcome |
| Phrill K  ([1](#_ENREF_1)) 2015 | USA | Tennessee Medicaid data linked to vital records | Yes | no | no | no | no | ++++strong | Yes based on mother claims \*\* | Good\*\*\* | used a 3-stage process  \*\*\* 8//9 |
| Vannappagari, V. 2016([2](#_ENREF_2)) | USA | Follow Up Data Registry | Yes  Exposure classification | yes | no | Yes | Yes | ++Low | \*\*\* somewhat representative\*  secure record\* | Can’t be ruled out effect of other intervention= 0 | \*\*\*  Registry & diagnostic base  Total =6 |
| Williams et.al.2016 ([3](#_ENREF_3)) | USA | Cohort  PHACS SMARTT study | no | YES | yes | No | no | +++  Strong | 2 drugs were used as HAART \*\* | Potential confounders like BMI cant be ruled out \*\* | Good\*\*\*7/9 |
| Townsend, CL2009([4](#_ENREF_4)) | UK and Ireland | longitudinal | No | no | no | No | no | ++++  Strong | \*\*\*  Some women were Included more than once | \*\*  injecting drug use (  ethnic origin,  maternal age at delivery & clinical status | \*\* \*\*  Registry & diagnostic base  9 |
| Sibiude, J, 2014([5](#_ENREF_5)) | French | Cohort | no | no | yes | no | yes | ++++  Strong | \*\*\* | \*\* | \*\*\*  8/9 |
| Watts DH, 2011([6](#_ENREF_6)) | US, Brazil, the Bahamas | Cohort | no | yes | no | no | yes | +++ Moderate | \*Use of registry  \* comparison group | preconception initiation of ART was not  distinguished from initiation after conception | \*multiple techniques used  \*\*Use of standard case definition 5/9 |
| Knapp, KM 2012. ([7](#_ENREF_7)) | US and Europe | Longitudinal | Yes, Control Group were not clearly stated | no | yes | no | no | +++ Moderate | \*Adequate Case defn  \*Drawn from same community  \*ascertainment of exposure  only 41 infants  with efavirenz exposure are included in this analysis. | - comparability not well discussed | - computerized screening  - recorded on clinical case  report forms - panel of clinicians who were  blinded to the mother’s ARV exposure during pregnancy. Deﬁn  itive  classiﬁcation of a congenital anomaly was made by  clinician consensus, using the Metropolitan Atlanta Congenital  Defects Program guidelines.  Total = 7/9 |
| Bera , 2010([8](#_ENREF_8)) | South Africa | Cohort | Yes, Classification bias | no | Yes | no | no | +++ Moderate | \*There were switching to NVP after grouping | \*\*pregnant woman were still on other HAART | \*\*\* U/S and Visual methods were used to ascertain  6/9 |
| Brogly, 2010([9](#_ENREF_9)) | USA | Cohort | No | no | no | no | Yes | ++++strong | \*\* from pro PACTG protocols 219 and 219C data | \*\*\* | \*\*\*Data measured every 3 months 8/9 |
| Zash R, 2016 ([10](#_ENREF_10)) | Botswana | Cohort | Yes | no | Yes  (nutrition status) | no | no | +++ Moderate | \*\*\*Adequate Case definition | \*Comparison group are on ZDV | \* Adverse pregnancy outcome instead of CA only |
| Joao, E. C. 2010([11](#_ENREF_11)) | Argentina  & Brazil | Cohort | No | no | Yes  (ART Grouping) | Yes | Yes | ++  Week | \*Adequate Case defn  \*Drawn from same community  \*ascertainment of exposure | \*Classification bias | \*\*Use of Computer +Ultrasound  Use of standard classification  5/9 |
| Berard, A.  2017([12](#_ENREF_12)) | Canada | Cohort ( Population based) | Yes  \*   inappropriate comparison group | No | no | yes | no | +++  Moderate | \*\*  population-based and collected many potential confounders. | \*   inappropriate comparison group  (significant imbalances in most background characteristics) | \*  No mention of which congenital classification criteria |
| Delicio, Adriane M. 2018  ([13](#_ENREF_13)) | Brazil | Cohort (Retrospective) | Yes  \*   inappropriate comparison group | Yes | Yes Children 0-5 years, Age difference | no | no | +++  Moderate | \*\* Large study  Retrospective | \*\* inappropriate comparison group | \*\* fair 6/9 |
| Van Dyke Dyke, 2016 ([14](#_ENREF_14)) | US, including Puerto Rico | Cohort | Not mentioned | Ye  S  The Objective was to study all outcomes | no | no | no | +++  Moderate | \*\*Not mentioned however large sample size and sufficient follow-up was used | \*\* | \*\*6/9 |
| Antiretroviral Pregnancy Registry Committee 2017([15](#_ENREF_15)) | USA | Longitudinal | Yes  \*  Passive report   inappropriate comparison group | no | Yes | Yes based on clinician reports | no | ++ week | Large data  \*\*  Selection bias | \*no standard comparison. Usually made with population data | \*\* based on clinician reports  5/9 |
| Mărdărescu M. 2013 ([16](#_ENREF_16)) | Romania | Cohort | Yes | no | Yes  Duration of diseases, BMI | no | no | +++Moderate | \*\* Smaller sample size, selection bias | \*\*fair | \*fair 6/9 |
| Zash, R 2019 ([17](#_ENREF_17)) | Botswana | Cohort | Yes  Follow up study | Yes  Other ARTs not placebo | Yes  Only Midwives so Clinical Exam | no | no | ++  Low | \*\*\* No matching | \*\* No matching | * Only Midwives do the clinical   6/9 |
| Williams 2015 ([18](#_ENREF_18)) | USA | Cohort Prospective | No | No | Yes | no | No | ++++  Strong | \*\*\*\* | \*\* | \*\*Outcome was based on document 8/9 |
| Townsend, CL2006  ([19](#_ENREF_19)) | UK and Ireland | longitudinal | No | no | no | No | no | ++++  Strong | \*\*\*  Some women were Included more than once | \*\*  injecting drug use (  ethnic origin,  maternal age at delivery & clinical status | \*\* \*  Registry & diagnostic base  7/9 |
| Prieto LM 2014([20](#_ENREF_20)) | Spain | Cohort | No | No | Yes. Use of Opiates | No | no | ++++  Strong | \*\*\* Women were included at any time | \*\* | \*\*\* European method of classification was used  8/9 |
| Bisio F, 2015 ([21](#_ENREF_21)) | Congo | Retrospective Cohort | Yes  Exposure classification | No | Yes. Other ARTs are also used | Yes | No | +++  Low | \*\* Women with NVP and other ART also includes | \* | \*\*No clear method of classification was used  5/9 |
| Patel D 2005 ([22](#_ENREF_22)) | Europe | Cohort | Yes ascertainment and reporting bias | No | No | No | No | ++++  Strong | \*\*\* ascertainment and reporting bias | \*\* | \*\* Reporting Bias  7/9 |
| Fernandez Ibieta M 2009([23](#_ENREF_23)) | Spain | Cohort | Yes  Analysis was  X2 or the Fisher test | Yes  It compares all ARTs | No | No | Yes  Wide CI and smaller comparison | ++ Week | \*\* Women with other ART also includes | * No clear comparison group | \*\*No clear method of classification was used  5/9 |
| Hankin CD 2006 ([24](#_ENREF_24)) | UK | Cohort | Yes  Document review | No | No | No | No | ++++  Strong | \*\*\* ascertainment and reporting bias | \*\* | \*\* Reporting Bias  7/9 |
| Brogly SB  2007  ([25](#_ENREF_25)) | USA | Cohort | Yes | No | Yes  confounding by maternal viral load and psychoactive drug use | No | No | +++  Moderate | \*\*  Exposure ascertainment  Controlling Confounding | \*\* | \*\*\* 7/9 |
| Tariq S etal. 2012([26](#_ENREF_26)) | Europe(European Collaborative study) | Cohort | Yes\*\*\* HAART for only at least 14 days rather than a month & Presence of other ARTs | Yes | No | No | No | +++Moderate | \*\*\* HAART for only at least 14 days rather than a month | \*other HAARTs also include | \*\* Data for significant 192 participants were missing 6/9 |
| Hill A etal. ([27](#_ENREF_27)) | 6 studies | Systematic review | Mix up of studies  And only 6 studies included | No | Yes | Yes | Yes some are studies by pharmacological companies | ++ week | \*\*  Compared at different exposure status.  Only two data bases searched | \*\* observational studies with out comparison | * Different outcome ascertainment 5/9 |
| Sibiude, J, etal. 2017([28](#_ENREF_28)) | French | Cohort | No | No | Yes other HAARTs | No | No | ++++  Strong | \*\*\*\* | \*Yes other HAARTs | \*\*Infected and uninfected children follow-up time  7/9 |

***\*Newcastle-Ottawa Assessment scale;*** *a study can be awarded a maximum number of stars within the selection, comparability and outcome categories. A maximum of 4 stars can be awarded for selection, 2 stars for comparability, and 3stars for outcome, a total score of 9 stars. We qualified studies with scores >5 to be methodologically fit****.***

***+ Grading was done according to the international GRADE group suggestion;****the system classifies quality of evidence (as reflected in confidence in estimates of effects) as high (Grade A ++++), moderate (Grade B++++), or low (Grade C++) according to factors that include the risk of bias, precision of estimates, the consistency of the results, and the directness of the evidence.*

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