Ferrand, RA; Briggs, D; Ferguson, J; Penazzato, M; Armstrong, A; MacPherson, P; Ross, DA; Kranzer, K (2016) Viral suppression in adolescents on antiretroviral treatment: review of the literature and critical appraisal of methodological challenges. Tropical medicine & international health, 21 (3). pp. 325-33. ISSN 1360-2276 DOI: https://doi.org/10.1111/tmi.12656

Downloaded from: http://researchonline.lshtm.ac.uk/2478671/

DOI: 10.1111/tmi.12656

Usage Guidelines

Please refer to usage guidelines at http://researchonline.lshtm.ac.uk/policies.html or alternatively contact researchonline@lshtm.ac.uk.

Available under license: http://creativecommons.org/licenses/by/2.5/
Review

Viral suppression in adolescents on antiretroviral treatment: review of the literature and critical appraisal of methodological challenges

Rashida A. Ferrand¹, Datonye Briggs¹, Jane Ferguson², Martina Penazzato², Alice Armstrong², Peter MacPherson³,4, David A. Ross¹ and Katharina Kranzer¹

¹ London School of Hygiene and Tropical Medicine, London, UK
² World Health Organization, Geneva, Switzerland
³ Department of Public Health and Policy, University of Liverpool, Liverpool, UK
⁴ Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK

Abstract

Objective Medication adherence is often suboptimal for adolescents with HIV, and establishing correct weight-based antiretroviral therapy dosing is difficult, contributing to virological failure. This review aimed to determine the proportion of adolescents achieving virological suppression after initiating ART.

Methods MEDLINE, EMBASE and Web of Science databases were searched. Studies published between January 2004 and September 2014 including ≥50 adolescents taking ART and reporting on the proportion of virologically suppressed participants were included.

Results From a total of 5316 potentially relevant citations, 20 studies were included. Only eight studies reported the proportion of adolescents that were virologically suppressed at a specified time point. The proportion of adolescents with virological suppression at 12 months ranged from 27 to 89%.

Conclusion Adolescent achievement of HIV virological suppression was highly variable. Improved reporting of virological outcomes from a wider range of settings is required to support efforts to improve HIV care and treatment for adolescents.

Keywords Adolescents, HIV, virological suppression

Introduction

An estimated 2.1 million adolescents (10–19 years of age) globally were living with HIV in 2012 [1]. HIV-related deaths among adolescents are estimated to have tripled since 2000, making HIV the second leading cause of death among adolescents worldwide [2]. Coverage of antiretroviral therapy (ART) is significantly lower (34%) in adolescents and children than in adults [3]. With successful scale-up of screening and treatment of infants infected with HIV, many of the >500 000 HIV-infected children who started on ART during infancy are surviving to adolescence, often with complex treatment needs.

Adolescence is accompanied by rapid physical, psychological and physiological changes which influence health-related behaviour. Adolescents frequently find consistent, long-term medication adherence difficult, and HIV treatment is no exception [4–6]. Maintaining sustained high levels of adherence to ART is the crux of successful treatment, preventing the development of drug resistance and disease progression, and decreasing risk of onward transmission once sexual debut occurs. Virological failure may also occur as a result of suboptimal drug dosing. Accurate weight-based dosing is difficult to achieve during the growth spurt which occurs in adolescence, and frequent dose changes are necessary, which may be challenging in under-staffed healthcare facilities in low-resource settings, where the majority of HIV-infected adolescents live, and can be confusing for the patient.

This review aimed to assess the proportion of adolescents taking ART in routine healthcare settings who achieve virological suppression in order to inform the need for interventions to optimise HIV outcomes in an age group that may be at high risk of treatment failure.
Methods

This review was conducted in accordance with the standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group [7]. A detailed protocol was prepared. We included cohort studies, randomised controlled trials (RCTs) and cross-sectional studies of adolescents taking ART that investigated the prevalence and/or rate of virological suppression. Studies were included if they reported on at least 50 HIV-infected adolescents (aged 10–19 years) receiving ART, or where the mean or median age of participants was between 10 and 19 years. Studies where neither the mean nor the median age was reported, or where data were not disaggregated by age, were excluded. No exclusions with regard to language or geographical area were applied.

A compound search strategy was developed (Table S1), and the following electronic databases were searched: Medline (OVID), Embase (OVID), Global Health (OVID) and Web of Science. Reference lists of all studies identified by the above methods, and bibliographies of relevant systematic reviews or meta-analyses were examined. All references were imported into EndNote (Thompson Reuters), and duplicates were removed. Titles and abstracts were examined independently by two reviewers (RF and KK) to exclude studies that clearly did not meet inclusion criteria.

The full text of all potentially relevant studies was obtained, and the inclusion criteria were applied using a pre-tested eligibility form. Data extraction was independently performed by two reviewers (RF and KK) using a standardised data extraction form. The following information was obtained for included studies: start and end dates of the study; study design; location (country, healthcare setting); rate/proportion of participants who died or were lost to follow-up; age; sex; CD4 cell count at ART initiation; ART regimen; median duration of follow-up; median duration on ART; laboratory method for HIV viral load measurement; viral load threshold used to define suppression; proportion of participants with viral load ascertained; proportion of participants with virological suppression at 12, 24, and 36 months; and overall proportion with virological suppression.

Primary outcomes were proportions of adolescents with suppressed viral load at 12 and 24 months of starting ART. Secondary outcomes included proportion with virological suppression irrespective of time on ART and rate of virological suppression. Virological suppression was defined as by the definitions used by the authors of the study.

A modified Newcastle-Ottawa Scale was used to assess the risk of bias [8]. A scoring scale to evaluate potential sources of bias was used. It included risk of selection bias; method of viral load testing; recording of baseline characteristics; duration of ART and follow-up; proportion of participants with missing outcomes; and appropriateness of analysis. Studies were scored on each of these criteria with studies graded as providing good (score 7–8), moderate (score 5–6) or low quality of evidence (3–4), or serious risk of bias (<3).

Results

From a total of 5316 potentially relevant unique citations, 20 studies were included in this review (Figure S1). Of the 20 studies that were included, 7 (35%) were from Africa [9–15], 8 (40%) were from North America [16–19] and Europe [20–23], 3 (15%) were from Asia [24–26] and 2 (10%) were from Latin America [27, 28] (Table 1). Half (n = 10) were cohort studies, and half were cross-sectional studies (n = 10). The studies were predominantly based on multicentre and/or multicountry research cohorts, or from urban, specialist centres. The cohorts included perinatally, sexually and parenterally infected adolescents.

Only eight studies reported the proportion of adolescents that were virologically suppressed at a specified time point: six [9–12, 21, 23], two [12, 15] and one [19] study reported the proportion who were virologically suppressed at 12, 24 and 36 months after ART initiation, respectively (Table 2). The remainder of the studies provided an overall proportion of virologically suppressed adolescents among those in care, without taking the duration of ART treatment into account.

In the six studies that reported this, the proportion of adolescents with virological suppression at 12 months after ART initiation varied from 27% to 89% (Table 2). Virological suppression rates in studies not stratified by duration on ART ranged between 28% and 87%. Approximately one-third of studies (n = 8) neither reported on the median duration on ART, nor on the median duration of follow-up [9, 14–16, 18, 19, 22, 23]. Four studies [15, 17, 18, 21] did not record the completeness of outcome data, and two studies had a very high proportion of missing viral load data (79% and 63%) [10, 19]. Overall most studies were scored as being moderate or low quality (Table 2).

Discussion

The main finding of this study was the paucity of data on virological outcomes among adolescents with HIV, despite more than 15 years of availability of combination ART. In included studies, there was substantial variation in the proportion of adolescents achieving virological suppression, and accurate overall estimates of the effectiveness of ART on viral suppression in this age group...
| Author, year       | Study period | Study setting                                                                 | Study design | N  | Age range (median age) | % Female | Mode of HIV acquisition | Median CD4 count at initiation (IQR), cells/µl | Median HIV viral load (log_{10}) at initiation (IQR) |
|--------------------|--------------|-------------------------------------------------------------------------------|--------------|----|------------------------|----------|-------------------------|-----------------------------------------------|-------------------------------------------------|
| **Africa**         |              |                                                                               |              |    |                        |          |                         |                                               |                                                 |
| Bakeera-Kitaka (2008) [9] | 2004–2006    | Uganda; Paediatric HIV Clinic, Mulago Hospital Public sector                  | Cohort       | 118| 10–19 years (13.6) at ART initiation | 64%      | Majority perinatal      | 124 (12–249)                                    | 5.4 (4.9–6.8)                                     |
| Evans (2013) [10]  | 2004–2010    | South Africa; Public sector HIV clinics; 5 urban Gauteng province; 2 rural Mpumalanga | Cohort       | 652| 10–19 years at ART initiation | 67%      | Mixed                   | 109 (24–195); 10–14 years 133 (54–198); 15–19 years | NR                                               |
| Ngdizi (2012) [11] | 2002–2009    | Cape Town, South Africa; Public sector community-based ART programme †         | Cohort       | 65 | 9–19 years (11.5) at cohort entry in 2009 | 66%      | Mixed: 72% perinatal, 6% sexual, 2% other | 134 (41–198)                                    | 4.8 (4.5–5.2)                                    |
| Nachega (2009) [12]| 1999–2006    | 9 countries in southern Africa; Private-sector, employer-subsidised disease management programme ‘Aid for AIDS’ | Cohort       | 154| 11–19 years (16.4) at ART initiation | 73%      | Sexual                  | 144 (27–246)                                    | 5.1 (4.5–5.6)                                    |
| Mutwa (2014) [13]  | 2009–2010    | Kigali, Rwanda; University Teaching hospital                                | CS           | 424| 1.7–18.8 years (10.8) at time of study | 52%      | Perinatal               | NR                                             | NR                                               |
| Sebunya (2013) [14]| 2004–2009    | Kampala, Uganda; JCRC-HIV care and research institution                      | Cohort       | 236| 10–18 years at ART initiation | NR       | Majority perinatal      | 135 (50–210); Unsuppressed 130 (44–262); Suppressed 127 (68–183) | NR                                               |
| Cutsem (2010) [15] | 2000–2007    | Cape Town, South Africa; Public sector primary care clinics supported by MSF | Cohort       | 86 | 10–19 years at ART initiation | NR       | NR                      | NR                                             |                                                 |
| Author, year | Study period | Study setting | Study design | N | Age range (median age) | % Female | Mode of HIV acquisition | Median CD4 count at initiation (IQR), cells/μl | Median HIV viral load (log_{10}) at initiation (IQR) |
|-------------|--------------|---------------|--------------|---|------------------------|----------|-------------------------|--------------------------------|--------------------------------------------|
| Asia        |              |               |              |   |                        |          |                         |                                    |                                            |
| Chokephaibulkit (2014) [25] | 2011 | 18 clinics in 6 Asian countries: TApHOD; public or university-based paediatric HIV referral clinics; urban/semi-urban | CS | 987 | 12–18 years at the last clinic visit | Perinatal | 160 (30–337); 12–14 years 98 (22–255) >>15 years | NR |
| Shet (2013) [26] | NR | Bangalore, India; tertiary care paediatric clinic | CS | 80 | 2–16 years (10) at time of study | Perinatal | 275 | NR |
| Zhao [24] (2011) † | 2006–2011 | Henan province, China; rural national programme | CS | 245 | 11–16 years (13.9) at time of study | 33% | 79% perinatal, 20% parenteral | NR |
| South and Central America |              |               |              |   |                        |          |                         |                                    |                                            |
| Santos Cruz (2011) [28] | 2002–2006 | 15 sites in Brazil, Mexico and Argentina; NISDI cohort | Cohort | 120 | 12–21 years (at time of enrolment into cohort) | 55% | 58% perinatal, 28% sexual, 8% transfusion, 6% unknown | NR |
| Santos Cruz (2014) [27] | 2009–2011 | 5 regions in Brazil | CS | 57 | 13–18 years at time of study | NR | Perinatal | NR |
| North America |              |               |              |   |                        |          |                         |                                    |                                            |
| Murphy (2005) [16] | 2003–2005 | 13 USA cities; REACH cohort | CS | 231 | 15–22 years (18.4) at time of study | 73% | Sexual | NR |
| Chandwani (2012) [17] | 2003–2005 | 5 clinics in Washington/Baltimore/New York; Adolescent Impact Study | CS | 104 | 13–21 years (16.4) at time of study | 54% | 75% perinatal, 25% other | NR |
| Van Dyke (2011) [18] | 2007–2009 | 15 sites USA; PHACS AMP Cohort USA: multicentre research cohort PACTG 381 | CS | 451 | 7–16 years (12.2) at time of study | Perinatal | CD4% 19 (12.25) | NR |
| Flynn (2007) [19] | 1999–2001 |  | Cohort | 120 | 11–22 years at ART initiation | 53% | Sexually-infected | NR |
| Author, year   | Study period | Study setting | Study design | N  | Age range (median age) | % Female | Mode of HIV acquisition | Median CD4 count at initiation (IQR), cells/μl | Median HIV viral load (log_{10}) at initiation (IQR) |
|---------------|--------------|---------------|--------------|----|------------------------|----------|------------------------|-----------------------------------------------|-------------------------------------------------|
| De Mulder (2012) [20] | 1997–2011 Madrid Cohort, Spain. Study at time of transfer to adult services | CS | 112 | Mean age: 18.9 years at time of study | 54% | 94% perinatal | <200: 64 (57%) 200–499: 37 (33%) >500: 11 (10%) | NR |
| Cohere (2008) [21] | 1998–2006 30 European countries | Cohort | 201 | 13–17 years (16.5) at time of study | 63% | 28% perinatal, 38% heterosexual, 4% IVDU, 3% gay | 222 (110, 340) | 4.8 (4.0, 5.2) |
| Dollfus (2010) [22] | 90 health centres, France; EPF/ANRS C010 cohort | CS | 210 | 10–17 years (15) at time of study | 50% | Perinatal | NR | NR |
| Judd (2007) [23] | 1997–2006 UK/Ireland Centres: CHIPS Cohort | Cohort | 141 | ≥10 years at ART initiation | NR | NR | NR | NR |

CD4 and VL at initiation of ART, except Nglazi: CD4/VL at cohort entry.
CS, Cross-sectional; ART, antiretroviral therapy; IVDU, intravenous drug user; NR, Not reported; JCRC, Joint Clinical Research centre, MSF, Medicine Sans Frontieres, TAPHOD, Treat Asia Pediatric HIV Observation Database, NISDI, NICHD International Site Development Initiative, REACH, Reaching for Excellence in Adolescence Care and Health, PHACS AMP, Pediatric HIV/AIDS Cohort Study, Adolescent Master Protocol, EPF/ANRS, French Perinatal Cohort, CHIPS, Collaborative HIV Pediatric Study.

*Adolescent-centred service (Nglazi: introduced 2008).
†Age, mode of acquisition, gender, duration of ART refer to only the 76 participants of 245 who had virological failure.
### Table 2: Virological outcomes in HIV-infected adolescents treated with antiretroviral therapy (ART)

| Study               | ART history & regimen | Median duration of follow-up | Median duration of ART | Virological suppression cut-off | Proportion of participant with viral load ascertained, % | Proportion virological suppressed, % | Overall proportion with virological suppression, % | Study quality |
|---------------------|-----------------------|-------------------------------|------------------------|--------------------------------|--------------------------------------------------------|--------------------------------------|-------------------------------------------------|--------------|
| Bakeera-Kitaka (2008) [9] | Naive; 96% NNRTI-based | NR                           | NR                    | <400                           | 72                                                     | 89                                   | ***                                              |             |
| Evans (2013) [10]      | Naive; 99% NNRTI-based | NR                           | 23.9 months: 10–14 years, 15.6 months: 15–19 years | <400                           | 21                                                     | 76                                   | ***                                              |             |
| Nglazi (2012) [11]     | Naive; 99% NNRTI-based | 34.6 months                  | NR                    | <400                           | 52                                                     | 27                                   | ***                                              |             |
| Nachega (2009) [12]    | Naive; 92% NNRTI-based | 27 months                    | NR                    | <400                           | 45, 25                                                  | 46, 44                                | ***                                              |             |
| Mutwa (2014) [13]      | On treatment; 99% NNRTI-based | 3.4 years                   | NR                    | <40                           | 85                                                     | 61                                   | ***                                              |             |
| Sebunya (2013) [14]    | On treatment; 100% NNRTI-based | NR                           | NR                    | <400                           | 67                                                     | 63                                   | ***                                              |             |
| Cutsem (2010) [15]     | Naive; NR 86% on 1st line treatment | NR                           | NR                    | <400                           | 84                                                     | 87                                   | **                                               |             |
| Zhao (2011) [24]       | On treatment; 100% NNRTI-based | NR                           | 6.0 years (4.3–7.5)   | <400                           | 84                                                     | 87                                   | **                                               |             |
| Shet (2013) [26]       | On treatment; 100% NNRTI-based | NT                           | 31 months             | <400                           | 82                                                     | 85                                   | ***                                              |             |
| Santos Cruz (2011) [28] | Treatment experienced; NR | 34 months: vertically infected, 35 months: horizontally infected | NR                    | <400                           | 97                                                     | 37.5                                  | **                                               |             |
| Santos Cruz (2014) [27] | Treatment experienced; NR | 7 years (mean)              | NR                    | <50                            | 53                                                     | 49                                   | **                                               |             |
| Flynn (2007) [19]      | Treatment experienced; NR | NR                           | <400                  | NR                             | 37                                                     | 66                                   | *                                                |             |
| Chandwani (2012) [17]  | Treatment experienced; NR | NR                           | 21% on ART for <1 years | <400                           | 28                                                     | 28                                   | *                                                |             |
| Murphy (2005) [16]     | Treatment experienced; NR | NR                           | NR                    | <40                            | 100                                                    | 69                                   | **                                               |             |
| Van Dyke (2011) [18]   | Highly treatment experienced; NR | NR                           | NR                    | NR                             | 68                                                     | 68                                   | **                                               |             |
cannot be drawn because of the variability and the low to moderate quality of most studies. Thus, a meta-analysis providing a pooled effect estimate was not attempted.

The studies included in this review illustrate some of the specific methodological issues encountered when analysing ART outcomes in children and adolescents, but also more general issues around analysis and reporting of ART outcomes. Any observational cohort study should be reported according to the STROBE (strengthening the reporting of observational studies in epidemiology) checklist, which has been endorsed by many high impact journals [29, 30]. The STROBE checklist recommends that for each explanatory and outcome variable, the source of data and the methods of assessment are clearly reported. Furthermore, the number of participants with missing data should be recorded and confounders taken into account [31].

Most of the studies included in this review did not provide all this information, hindering our ability to accurately identify the proportion of adolescents succeeding on ART. The responsibility of accurate reporting lies not only with the authors, but also with the wider scientific community including journal editors and peer reviewers. Some of the studies included in this review were published before the STROBE checklist was developed.

Even more critical is the fact that a number of the included cross-sectional studies provided point estimates of viral load suppression without stratifying the results by time on ART. Several of these studies did not even report the mean or median time on ART [14, 16–18, 22]. Time on ART is highly likely to act as a confounder and cohorts with similar success rates, but different follow-up times will appear to have different virological suppression rates. Thus, unstratified point prevalence estimates of virological suppression are meaningless, and we urge researchers to report results stratified by duration on ART in all future studies.

All included studies classified participants as adolescents according to their age at initiation of ART. A child aged 14 on the basis of having started ART at a child aged 14 a decade or so ago has been taking ART for over 14 years old. Clinicians are unlikely to assess ART for a few months or several years, or over a decade. Clinicians are unlikely to assess the likelihood of virological suppression in children of a 14-year-old based on ART results stratified by duration on ART in all future studies. ART is highly likely to act as a confounder and cohorts with similar success rates, but different follow-up times will appear to have different virological suppression rates. Thus, unstratified point prevalence estimates of virological suppression are meaningless, and we urge researchers to report results stratified by time on ART in all future studies. Several of these studies did not even report the mean or median time on ART [14, 16–18, 22]. Time on ART is highly likely to act as a confounder and cohorts with similar success rates, but different follow-up times will appear to have different virological suppression rates. Thus, unstratified point prevalence estimates of virological suppression are meaningless, and we urge researchers to report results stratified by time on ART in all future studies. Several of these studies did not even report the mean or median time on ART [14, 16–18, 22]. Time on ART is highly likely to act as a confounder and cohorts with similar success rates, but different follow-up times will appear to have different virological suppression rates. Thus, unstratified point prevalence estimates of virological suppression are meaningless, and we urge researchers to report results stratified by time on ART in all future studies. Several of these studies did not even report the mean or median time on ART [14, 16–18, 22]. Time on ART is highly likely to act as a confounder and cohorts with similar success rates, but different follow-up times will appear to have different virological suppression rates. Thus, unstratified point prevalence estimates of virological suppression are meaningless, and we urge researchers to report results stratified by time on ART in all future studies.
information can only be obtained if age-updated analyses are performed, alongside the analyses stratified by time on treatment discussed above.

A total of 21 studies included more than 50 adolescents on ART and reported on virological suppression, but did not provide adolescent-specific suppression estimates but analysed adolescents together with children, which meant they had to be excluded. These studies could have contributed substantially to the body of evidence if age-specific estimates had been provided. Furthermore, systematic reviews focus on peer-reviewed published studies and thus are subject to publication bias. Due to heterogeneity of study designs and outcome definitions, summary estimates could not be calculated. Viral load testing methods have evolved over time, which makes comparison of studies across different periods and settings challenging. Further limitations of this review are the quality of studies included and high levels of missing data in some studies.

In conclusion, most available estimates of viral load suppression in adolescents are not very informative due to serious methodological concerns. Authors, journals and peer reviewers should be encouraged to follow the recommendation for observational cohort studies as laid out by the STROBE statement. We recommend the development of guidelines for ART cohort reporting focused on children, and adolescents to ensure data are analysed using generally accepted age groups such as 0, 1–4, 5–9, 10–14, 15–19 years, that time on ART is taken into account through stratified analyses, and that age-updated analyses are conducted.

Acknowledgement

This work was commissioned by the World Health Organization. The content is solely the responsibility of the authors and does not necessarily represent the official views of the World Health Organization. RAF is funded by the Wellcome Trust.

References

1. World Health Organization. Adolescent HIV Testing, Counselling and Care: Implementation Guidance for Health Providers and Planners. World Health Organization: Geneva, Switzerland, 2014.
2. World Health Organization. Health for the World’s Adolescents: A Second Chance in the Second Decade. World Health Organization: Geneva, Switzerland, 2014.
3. World Health Organization. Global Update on HIV Treatment 2013: Results, Impact and Opportunities. World Health Organization: Geneva, 2013.
4. Hanghøj S, Boisen KA. Self-reported barriers to medication adherence among chronically ill adolescents: a systematic review. J Adolesc Health 2014: 54: 121–138.
5. Modi AC, Pai AL, Hommel KA et al. Pediatric self-management: a framework for research, practice, and policy. Pediatrics 2012: 129: e473–e485.
6. Mofenson LM, Cotton MF. The challenges of success: adolescents with perinatal HIV infection. J Int AIDS Soc 2013: 16: 1650.
7. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009: 6: e1000097.
8. Wells GA, Shea B, O’Connell D et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. O.H.R.L.: Ottawa, ON, 2007.
9. Bakeera-Kitaka S, McKellar M, Snider C et al. Antiretroviral therapy for HIV-1 infected adolescents in Uganda: assessing the impact on growth and sexual maturation. J Pediatr Infect Dis 2008: 3: 97–104.
10. Evans D, Menezes C, Mahomed K et al. Treatment outcomes of HIV-infected adolescents attending public-sector HIV clinics across Gauteng and Mpumalanga, South Africa. AIDS Res Hum Retroviruses 2013: 29: 892–900.
11. Nglazi MD, Kranzer K, Hole P et al. Treatment outcomes in HIV-infected adolescents attending a community-based antiretroviral therapy clinic in South Africa. BMC Infect Dis 2012: 12: 21.
12. Nachega JB, Hislop M, Nguyen H et al. Antiretroviral therapy adherence, virologic and immunologic outcomes in adolescents compared with adults in southern Africa. J Acquir Immune Defic Syndr 2009: 51: 65–71.
13. Mutwa PR, Boer KR, Rusine J et al. Long-term effectiveness of combination antiretroviral therapy and prevalence of HIV drug resistance in HIV-1 infected children and adolescents in Rwanda. Pediatr Infect Dis J 2014: 33: 63–69.
14. Sebunya R, Musiime V, Kitaka SB, NdeezI G. Incidence and risk factors for first line anti retroviral treatment failure among Ugandan children attending an urban HIV clinic. AIDS Res Ther 2013: 10: 25.
15. Van Cutsem G, Knight L, Abrahams M et al. Outcomes in children, adolescent, youth and adults on ART in Khayelitsha. abstract no THPE0170. XVIII International AIDS Conference 2010, Vienna, Austria.
16. Murphy DA, Belzer M, Durako SJ et al. Longitudinal antiretroviral adherence among adolescents infected with human immunodeficiency virus. Arch Pediatr Adolesc Med 2005: 159: 764–770.
17. Chandwani S, Koenig LJ, Sill AM, Abramowitz S, Conner LC, D’Angelo L. Predictors of antiretroviral medication adherence among a diverse cohort of adolescents with HIV. J Adolesc Health 2012: 51: 242–251.
18. Van Dyke RB, Patel K, Siberry GK et al. Antiretroviral treatment of US children with perinatally acquired HIV infection: temporal changes in therapy between 1991 and
2009 and predictors of immunologic and virologic outcomes. *J Acquir Immune Defic Syndr* 2011: 57: 165–173.

19. Flynn PM, Rudy BJ, Lindsey JC *et al.* Long-term observation of adolescents initiating HAART therapy: three-year follow-up. *AIDS Res Hum Retroviruses* 2007: 23: 1208–1214.

20. de Mulder M, Yebra G, Navas A *et al.* High drug resistance prevalence among vertically HIV-infected patients transferred from pediatric care to adult units in Spain. *PLoS ONE* 2012: 7: e52155.

21. Sabin CA, Smith CJ, d’Arminio MA *et al.* Response to combination antiretroviral therapy: variation by age - The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study group. *Aids* 2008: 22: 1463–1473.

22. Dollfus C, Le Chenadec J, Faye A *et al.* Long-term outcomes in adolescents perinatally infected with HIV-1 and followed up since birth in the French perinatal cohort (EPF/ANRS CO10). *Clin Infect Dis* 2010: 51: 214–224.

23. Judd A, Doerholt K, Tookey PA *et al.* Morbidity, mortality, and response to treatment by children in the United Kingdom and Ireland with perinatally acquired HIV infection during 1996-2006: planning for teenage and adult care. *Clin Infect Dis* 2007: 45: 918–924.

24. Zhao Y, Mu W, Harwell J *et al.* Drug resistance profiles among HIV-1-infected children experiencing delayed switch and 12-month efficacy after using second-line antiretroviral therapy: an observational cohort study in rural China. *J Acquir Immune Defic Syndr* 2011: 58: 47–53.

25. Chokephaibulkit K, Kariminia A, Oberdorfer P *et al.* Characterizing HIV manifestations and treatment outcomes of perinatally infected adolescents in Asia. *Pediatric Infect Dis J* 2014: 33: 291–294.

26. Shet A, Neogi U, Sahoo PN, De Costa A Effectiveness of first-line antiretroviral therapy and acquired drug resistance among HIV-1-infected children in India. *Pediatric Infect Dis J* 2013: 32: e227–e229.

27. Cruz ML, Cardoso CA, Darmont MQ *et al.* Viral suppression and adherence among HIV-infected children and adolescents on antiretroviral therapy: results of a multicenter study. *J Pediatr (Rio J)* 2014: 90: 563–571.

28. Santos Cruz ML, Freimanis Hance L, Korelitz J *et al.* Characteristics of HIV infected adolescents in Latin America: results from the NISDI pediatric study. *J Trop Pediatr* 2011: 57: 165–172.

29. The PLOS Medicine Editors Observational Studies: Getting Clear about Transparency. *PLoS Med* (2014) 11, e1001711.

30. Field N, Cohen T, Struelens MJ *et al.* Strengthening the Reporting of Molecular Epidemiology for Infectious Diseases (STROME-ID): an extension of the STROBE statement. *Lancet Infect Dis* 2014: 14: 341–352.

31. Grimsrud AT, Cornell M, Egger M, Boulle A, Myer L Impact of definitions of loss to follow-up (LTFU) in antiretroviral therapy program evaluation: variation in the definition can have an appreciable impact on estimated proportions of LTFU. *J Clin Epidemiol* 2013: 66: 1006–1013.

**Supporting Information**

Additional Supporting Information may be found in the online version of this article:

Figure S1 Selection process for the inclusion of studies.

Table S1 Search strategy for Medline, Embase and Global Health.

**Corresponding Author** Rashida A. Ferrand, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK. E-mail: rashida.ferrand@lshtm.ac.uk

© 2015 The Authors. Tropical Medicine & International Health Published by John Wiley & Sons Ltd.