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Notes to the Field: The Lit Digest
A digest of recent HIV/AIDS intervention literature,
relevant to resource-limited settings

This literature digest summarizes, contextualizes and assesses the quality of recently published studies of behavioral, policy and prevention interventions that have one or more of the following aims: to reduce sexual or drug-related HIV risk behaviors, to decrease primary or secondary HIV transmission, to improve health service delivery and quality of life, or to improve HIV treatment and treatment adherence. Included studies were conducted in or have applications to resource-limited settings. The Lit Digest is prepared by the Cochrane HIV/AIDS Group, based at the University of California, San Francisco. An archive of the Lit Digest from 2006 to the present can be found here: http://hivinsite.ucsf.edu/InSite?page=jl-00-00

SUMMARIZED IN THIS EDITION:

Antiretroviral therapy

Pediatric antiretroviral therapy


Prevention of mother-to-child HIV transmission (PMTCT)

References for all summaries begin on page 10.
Antiretroviral therapy


OBJECTIVE: To assess the comparative efficacy of lamivudine (3TC) and emtricitabine (FTC) as components of combination antiretroviral therapy (ART)

STUDIES: Randomized controlled trials (RCTs) and quasi-RCTs.

POPULATION: Treatment-naïve or treatment-experienced HIV-infected adult patients.

INTERVENTION: Trials in which 3TC or FTC were a component of three-drug ART. Reviewers only included trials where partner drugs in the regimen were identical or could be considered to be comparable. Reviewers excluded studies in which different trial arms used partner drugs with established differences in safety or efficacy.

MAIN OUTCOME MEASURES: Virologic suppression, resistance mutations and adverse events.

SEARCHES, SCREENING AND DATA EXTRACTION: In addition to searching MEDLINE for all trials including 3TC or FTC in one arm (with the aim of potentially comparing such trials indirectly through a network meta-analysis), reviewers searched MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews for trials in which comparable regimens that included 3TC or FTC were assessed for virologic efficacy. Databases were searched through June 30, 2013. Reviewers also searched abstracts from all International AIDS Society conferences through 2013. There were no limits to language or publication status. Two reviewers working independently screened 2,871 references and closely examined 38 full-text articles. Data were extracted by one reviewer and independently verified by a second reviewer.

RESULTS: Twelve articles met the review’s inclusion criteria, comprising 15 different randomized comparisons that provided data on 2,251 patients receiving 3TC and 2,662 patients receiving FTC. Studies were published between 2002 and 2013. Five trials were conducted in ART-naïve patients. In all but three trials whose comparisons included the same backbone regimens in each arm, studies compared tenofovir (TDF)-based regimens to abacavir (ABC)-based regimens. Two trials included some patients with high viral loads at baseline (≥100,000 copies/mL); only the results for those patients in the low viral load strata (<100,000 copies/mL) were included in the reviewers’ meta-analysis.

Treatment success: Overall, treatment success between 3TC and FTC was not significantly different (relative risk [RR] 1.00, 95% confidence interval [CI] 0.97 to 1.02). No heterogeneity was observed ($I^2=0$). In the three trials directly comparing 3TC and FTC, the difference was also non-significant (RR 1.03, 95% CI 0.96 to 1.10, $p=0.3$). Subgroup analyses and random effects meta-analytic methods did not change the significance of this outcome.

Antiretroviral resistance: Reviewers identified four trials that provided data on the emergence of M184V resistance mutations among virologically failing patients (n=234). Two of these trials genotyped all patients experiencing virologic failure and found no difference by regimen. The other two trials reporting resistance data did so only on a subset of virologically failing patients, and these studies reported an increased risk of M184V resistance mutation development among patients receiving lamivudine. The overall pooled estimate, using a random-effects model, was not significant (RR 1.4, 95% CI 0.6 to 3.3) but the reviewers caution that this result should be interpreted carefully due to high heterogeneity ($I^2 = 80\%$) and the selective reporting of the outcome in some of the trials.

Adverse events: Two of the three trials with identical backbone regimens provided data on adverse events. In one trial, no difference in the incidence of any grade 3 or 4 adverse event was reported. In the other trial, 4% of patients discontinued treatment due to adverse events in the FTC arm and there were no discontinuations in the 3TC arm.

CONCLUSIONS: The reviewers conclude that consistent with very similar chemical structure of these two nucleoside analogues, there are no significant differences in the efficacy of 3TC and FTC. They caution, however, that because they included studies with non-identical background regimens, and because of sparse data in regard to viral mutations, the results of the review should not be understood as definitive evidence of equivalence.
QUALITY OF THE EVIDENCE: The reviewers used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology1 to assess evidence quality. GRADE ranks the quality of evidence on four levels: "high," "moderate," "low" and "very low." Evidence from randomised controlled trials starts at "high," but can be downgraded for study limitations (risk of bias), inconsistency of results, indirectness of evidence, imprecision or for reporting bias. Evidence from observational studies starts at "low," but can be upgraded if the magnitude of treatment effect is very large, if there is a significant dose-response relation, or if all possible confounders would decrease the magnitude of an apparent treatment effect. Evidence from observational studies can also be downgraded. The reviewers found the quality of the evidence overall, across outcomes, to be moderate. Risk of bias was judged to be low and there was no evidence of publication bias. Results of all studies were consistent for the critical outcomes of virologic suppression and failure. The reviewers note their concern about indirectness in the context of including trials with non-identical backbone regimens, but felt that the direction of this bias would be expected to favor FTC.

QUALITY OF THE REVIEW: This was a high quality systematic review. It meets every relevant criterion of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.2

IN CONTEXT: 3TC and FTC are both used as core components of dual nucleoside reverse transcriptase inhibitor (NRTI) first-line ART backbone regimens. Although from a clinical and programmatic perspective they have been considered to be interchangeable,3,4 limited data from early in vitro studies had suggested inferior virologic efficacy of 3TC.5,6 This presumption was recently applied to cost-effectiveness analyses.7 This review makes clear that 3TC and FTC are clinically comparable in efficacy.

PROGRAMMATIC IMPLICATIONS: Following the recommendations of current national and international treatment guidelines,3,4 3TC and FTC can be regarded as interchangeable.

Pediatric antiretroviral therapy


OBJECTIVE: To identify predictors of mortality, including under-nutrition, in HIV-infected children beginning antiretroviral therapy (ART).

SETTING: Dar es Salaam, Tanzania.

STUDY DESIGN: Prospective cohort study.

POPULATION: Children (≤15 years) initiating ART in the Management and Development for Health (MDH) program from October 2004 through December 2010. The MDH is a Tanzanian non-governmental organization (NGO) providing HIV/AIDS care and treatment services.

INTERVENTION (PREDICTOR VARIABLE): Baseline nutritional status.

MAIN OUTCOME MEASURES: All-cause mortality; standardized weight-for-age Z scores (WAZ), height-for age Z scores (HAZ), weight-for-height/length Z scores (WHZ; for children aged ≤2 years), and body mass index Z scores (BMIZ; for children aged >2 years).

METHODS: Children presenting with World Health Organization (WHO) clinical stage IV or III disease, regardless of absolute CD4 count or percentage, or WHO stage I or II disease and severe immunodeficiency, were eligible for ART. Initial ART regimens included at least two nucleoside reverse transcriptase inhibitors (NRTI) and one non-nucleoside reverse transcriptase inhibitor (NNRTI), or two NRTIs and one protease inhibitor. Patients also received prophylaxis and treatment of opportunistic infections and other conditions.

Children were evaluated at outpatient clinics each month, receiving a physician’s examination, adherence and nutrition counseling, and medication refills. Comprehensive laboratory panels, including assessment of CD4 cell counts, were performed every four months. Children with tuberculosis (TB) at baseline were treated according to Tanzania’s national guidelines.
Investigators assessed weight and growth parameters using standard methods, and calculated scores using WHO’s Child Growth Standards. Standard mid-upper-arm circumference (MUAC) parameters in children aged >5 years were additionally calculated using an adaptation of United States data.

Investigators recorded child deaths upon notification by family members, friends or other project colleagues. Early mortality was defined as death with the first 90 days of ART initiation. Overall mortality was defined as death any time after ART initiation.

In each stratum of child nutritional status, investigators used Kaplan-Meier curves to estimate time to death. Investigators examined the relative associations with mortality of baseline nutritional status, change in nutritional status within the first 90 days and other baseline characteristics, using the Cox proportional hazards model for time. Children’s data were censored at the end of study if they were event-free, or if they were so at their last visit. Investigators adjusted models using variables of nutrition status, calendar year, level of immune suppression, WHO disease stage, history of TB, opportunistic infections, ART regimen, district of residence, cotrimoxazole use, season of ART initiation (i.e. long dry, short dry, long rainy or short rainy), and the child’s sex.

RESULTS: Between October 2004 and December 2010, a total of 3,180 children initiated ART. Data from 3,144 children were considered in the analyses. The prevalence of child undernutrition at ART initiation was high, with 1,275 (53%) of the children underweight, 990 (33%) wasted, 1,673 (56%) stunted, and 1,222 (39%) with low MUAC. All children were initiated on recommended first-line ART regimens, about half (n=1,075, 52%) of which comprised zidovudine (AZT) plus lamivudine (3TC) plus nevirapine (NVP). More than a third (n=761, 37%) of children received regimens that contained stavudine (d4t). Few (n=356, 17%) children received regimens containing efavirenz (EFV).

During six years of follow up, 268 children died (cumulative mortality=12.4%) More than half (n=151, 56.3%) died within 90 days of initiating ART. At three, 12, 24 and 60 months respectively, cumulative mortality rates were 4.8%, 7.3%, 8.2% and 8.5%. Cumulative loss to follow-up (LTFU) rates at three, 12, 36, and 60 months respectively were 10.6%, 21.1%, 30.8%, and 58.2%.

Nutritional status was significantly associated with mortality. Death rates overall were highest among children with WAZ ≤-3 compared with those with WAZ >-1 (p<.0001). Compared to children with WAZ >-1, children with WAZ from ≤-2 to < -3 had nearly double the risk of death (relative risk [RR], 1.85, 95% confidence interval [CI] 1.10 to 3.11). The risk was more than tripled (RR 3.36, 95% CI 2.12 to 5.32) in children who were severely underweight (WAZ ≤-3). For deaths that occurred in the first 90 days after ART initiation, compared to children with WAZ >-1, those with WAZ from ≤ -2 to < -3 had more than twice the risk of death (RR, 2.51, 95%CI 1.05 to 5.95). The risk was more than seven-fold (RR 7.12, 95% CI 3.33 to 15.22) in those who were severely underweight. Similarly, WHZ or BMIZ of ≤-2 were associated with a significantly increased risk of mortality, nearly triple the risk (RR 2.94, 95% CI 2.14 to 4.03) for overall mortality, and more than five-fold (RR 5.80, 95% CI 3.65 to 9.22) for mortality in the first 90 days after ART initiation.

Children with HAZ of ≤-1 were at nearly twice the risk of dying in the first 90 days (RR 1.90, 95% CI 1.03 to 3.50) and overall (RR 1.92, 95% CI 1.23 to 3.00). Children with MUAC of ≤11.5 cm were also at much greater risk of dying in the first 90 days (RR 6.29, 95% CI 3.62 to 10.96) and overall (RR 3.87, 95% CI 2.63 to 5.70).

Baseline variables (apart from nutritional status) contributing significantly to overall mortality risk:

- **Having opportunistic infections**: RR 2.23, 95% CI 1.61 to 3.09
- **History of TB**: RR 1.55, 95% CI 1.09 to 2.18
- **HIV disease stage III at ART initiation**: RR 1.85, 95% CI 1.05 to 3.27
- **HIV disease stage IV at ART initiation**: RR 2.43, 95% CI 1.33 to 4.42
- **Living in the Temeke district of Dar es Salaam**: RR 1.58, 95% CI 1.18 to 2.11
- **Severe anemia**: RR 1.91 95% CI 1.21 to 2.99
- **Severe immune suppression**: RR 1.46, 95% CI 1.07 to 2.00

Child’s sex, initial ART regimen, season of ART initiation, and use of cotrimoxazole were not significantly associated with overall mortality risk.
CONCLUSIONS: The investigators conclude that child undernutrition at the time of ART initiation was associated with increased mortality, particularly during the first 90 days.

RISK OF BIAS: The risk of bias in this observational cohort study is moderate to high. The sample size was large (n=3,144) and was likely to have been representative. Follow-up time (six years) was sufficient. Investigators were unable to adjust for potential confounders including maternal factors and viral load. LTFU overall was very high (58.2%). At 90 days, however, the rate of LTFU was much less severe (10.6%) and was within usual bounds of acceptability. Estimates for early mortality outcomes may be more reliable.

IN CONTEXT: This study’s findings with regard to early and cumulative mortality are consistent with those of earlier studies. A Zambian study, with a somewhat older sample, found a somewhat lower (8.3%) cumulative mortality but a very similar (56.6%) early mortality. A smaller, briefer study in Haiti also found a lower (9%) overall mortality, and had a somewhat higher (61%) early mortality.

PROGRAMMATIC IMPLICATIONS: In addition to ART, children with HIV should receive appropriate nutritional monitoring and support. In studies of adult populations, macronutrient supplementation has been efficacious in improving outcomes, and should be considered for pediatric populations.


OBJECTIVE: To assess the evidence for the optimal time to initiate combination (three-drug) antiretroviral therapy (ART) in treatment-naive, HIV-infected children aged two to five years.

STUDIES: Randomized controlled trials (RCTs) and prospective cohort studies that followed children from enrollment to ART initiation, and for at least a median of one year on ART.
POPULATION: Children with confirmed HIV infection aged between 24 and 59 months (two to five years of age) who were treatment-naïve at enrollment (apart from those exposed to antiretroviral prophylaxis for preventing mother-to-child HIV transmission).

INTERVENTION: Studies comparing ART initiation at different thresholds. In RCTs the intervention group must have initiated ART irrespective of clinical stage or CD4 count (immediate initiation). The control group must have initiated ART using clinical and immunological criteria to determine the time for initiation (deferred initiation) as recommended at the time of the study. Cohort studies must have compared children starting ART at different CD4 percentages or CD4 counts. Analyses must have included adjustment for time-dependent confounding and lead-time bias specifically to evaluate the effect on outcomes of ART initiation timing.

MAIN OUTCOME MEASURES: Mortality; death or AIDS; time to death or AIDS; immunologic response; adherence; loss to follow-up (LTFU); virologic response; HIV drug resistance; severe adverse events (SAE).

SEARCH STRATEGY: Standard Cochrane HIV/AIDS Group search strategies were used, along with a range of relevant keywords and medical subject heading (MeSH) terms. There were no limits to language or publication status. Databases searched included the Cochrane Central Register of Controlled Trials, EMBASE, and PubMed, as well as online archives of major HIV/AIDS conference abstracts. The date range for the searches of the peer-reviewed literature was from January 1980 to July 2012. Archived conference abstracts were searched from 1985 to 2012. The World Health Organization (WHO)’s International Clinical Trials Registry Platform (ICTRP) and the National Institutes of Health’s “ClinicalTrials.gov” were also searched for ongoing trials. The reviewers checked reference lists of included trials, and contacted researchers in the field as well as policy makers at the World Health Organization (WHO) and other inter-governmental organizations.

SEARCHES, SCREENING AND DATA EXTRACTION: After removing duplicate references, 1,475 records were retrieved. Standard Cochrane methods were used in the screening process and in data collection. Two reviewers working independently excluded 1,421 records (96.3%). Fifty-four full-text articles were obtained for closer scrutiny. Three studies (two RCTs and one cohort study) met the review’s inclusion criteria. Two reviewers working independently extracted data from included studies, using a standardized form.

RESULTS: Two small RCTs evaluated the effects in children aged one to 12 years of immediate ART initiation at CD4 cell percentage of between 15% and 25%, compared with deferring ART until pre-defined immunological and clinical thresholds. No differences in outcomes were noted between the randomized groups. One cohort study compared delaying ART in HIV and tuberculosis (TB) co-infected children with ART initiation soon after commencing TB treatment. Delaying ART initiation to later than 15 days after commencing TB treatment was protective against death, but this effect was reduced at 30 days. It was potentially harmful if ART was deferred beyond 60 days. None of the studies exclusively included children within the specific focus age of two to five years. The RCTs were conducted in Thailand and Cambodia, and the cohort study was conducted in South Africa. One RCT, Ananworanich 2008, was an initial feasibility study (n=43) for the larger second RCT, the “PREDICT” trial (n=300). Median participant age in Anananworanich 2008 was 4.8 years (interquartile range [IQR] 2.7 years to 6.6 years). In the PREDICT trial (Wongsawat 2010, plus unpublished data that the reviewers obtained in 2012 from PREDICT investigators), 88/150 (59%) and 83/150 (55%) of participants in the immediate and deferred treatment groups respectively were aged one to six years. ART in the trials ART comprised standard doses of generic individual zidovudine (AZT), lamivudine (3TC) and nevirapine (NVP). The cohort study (n=573) included children aged one to 15 years with a median age of 3.5 years (IQR 1.4 years to 6.8 years). Although the median length of follow-up in this study was 9.6 months (IQR 1.9 months to 23.1 months), less than the review’s pre-specified median one year follow-up, the reviewers included it because data on ART initiation in HIV and TB co-infected children are so sparse. First-line ART regimen in the cohort study comprised stavudine (d4T), lamivudine (3TC), and ritonavir (RTV)-boosted lopinavir (LPV/r) for children aged ≤3 years; or d4T, 3TC and efavirenz (EFV) for those >3 years and weighing more than 10 kilograms. Double doses of RTV were given during anti-TB treatment. All children were receiving TB treatment which comprised a combination of rifampicin (RIF), isoniazid (INH), and pyrazinamide (PZA) for the initial two months followed by RIF and INH for the remaining four months.

Primary outcome:
Mortality: In the PREDICT trial, one child (1/150) in the immediate treatment group died (risk ratio [RR] 3.00, 95% confidence interval [CI] 0.12 to 73.06). This child (1/48) was in a subgroup of children aged 24 to 59 months. Statistically, however, this event was not significant.

In the cohort study, death was compared in three different time periods: 1) ART initiation after 15 days following TB treatment vs. initiation within 15 days following TB treatment; 2) ART initiation after 30 days following TB treatment vs. initiation within 30 days; and 3) ART initiation after 60 days following TB treatment vs. within 60 days. The reviewers do not provide the number of actual deaths within the respective time periods, but provide the study investigators’ weighted hazard ratio (HR) for death in each time period, accounting for time-dependent level of immunosuppression, viral load, weight-for-age Z score and age at TB treatment initiation.

- More than 15 days vs. less than 15 days: HR 0.82, 95% CI 0.48 to 1.41
- More than 30 days vs. less than 30 days: HR 0.86, 95% CI 0.46 to 1.60
- More than 30 days vs. less than 30 days: HR 1.32, 95% CI 0.55 to 3.16

Secondary outcomes:

Death or AIDS-defining illness (Centers for Disease Control and prevention [CDC] Clinical Category C, severely symptomatic disease or Category B, moderately symptomatic disease\textsuperscript{3,5}): No children in Ananworanich 2008 developed CDC Category C disease. In the PREDICT trial, three children in the immediate treatment group developed Category C disease (Pneumocystis jiroveci pneumonia, n=1; pneumonia/sepsis leading to death, n=1; disseminated penicilliosis, n=1). Two children in the deferred treatment group developed Category C disease (esophageal candidiasis, n=1; extrapulmonary TB, n=1). The RR for Category C disease was 1.50 (95% CI 0.25 to 8.85; p=0.65). In subgroup analysis of the 24 to 59 month age group (n=95) in the PREDICT trial, in both treatment groups, the RR was 0.96 (95% CI: 0.06, 14.87; p=0.98). The reviewers combined data from both trials for children in all age groups using the random effects model. The RR for Category C disease for all ages across both treatment groups was 1.42 (95% CI 0.14 to 14.28; p=0.77).

Categorizing pulmonary TB as CDC Category B disease, the reviewers found a non-significantly higher risk of Category B disease across both trials of Category B disease in the immediate treatment group (RR 1.42, 95% CI 0.14 to 14.28, p=0.77). Because of high heterogeneity (\(\chi^2=2.84\), degrees of freedom [df]=1, p=0.09, I\(^2\)=65%) the reviewers performed sensitivity analysis and re-analyzed the data using the Peto odds ratio (POR). The POR in the new analysis was 0.70 (95% CI 0.39 to 1.24, p=0.22), suggesting that children in the immediate treatment group had 30% non-significantly lower odds of developing Category B disease. Heterogeneity remained very high (\(\chi^2=5.22\), df=1, p=0.02, I\(^2\)=81%). In the subgroup of children aged 24 to 59 months, the results were similar (POR 0.76, 95% CI 0.29 to 2.02, p=0.59).

Pulmonary TB: In meta-analysis of the 24 to 59 month age groups in both trials (immediate, n=59; deferred, n=63), one case of pulmonary TB was observed in each group (RR=1.19, 95% CI 0.19 to 7.27; p=0.85) with low heterogeneity (\(\chi^2=1.36\), df=1, p=0.24, I\(^2\)=26%).

Median time before development of Category B or Category C events: Both trials reported on the median time before development of either CDC Category B or Category C events for children of all age groups. In Ananworanich 2008, events in the immediate treatment group occurred after a median of 60 weeks (IQR 48 weeks to 72 weeks). No events occurred in the deferred treatment group. In the PREDICT trial, events occurred after a median of nine weeks (IQR 4 weeks to 30 weeks) in the immediate treatment group compared to 57 weeks (IQR 34 weeks to 101 weeks) in the deferred treatment group.

Proportion of children with virologic suppression (HIV RNA <50 copies/mL): In random effects meta-analysis of data from both trials, there was no difference between the immediate and deferred treatment groups in the proportion of children with virologic suppression (RR 0.96, 95% CI 0.84 to 1.09, p=0.52). There was no statistical heterogeneity (\(\chi^2=0.29\), df=1; p=0.59; I\(^2\)=0%). In subgroup analysis of the 24 to 59 month age group in the PREDICT trial only, the results were similar to that for all age groups (RR 1.11, 95%CI 0.86 to 1.43, p=0.43).

Proportion of children with virologic suppression (HIV RNA <400 copies/mL): Yotebieng 2010 assessed virologic suppression in 324/461 (70%) of children who initiated ART and who had at least one viral load measurement after
cART initiation. The results were analyzed in the same three time-periods as for mortality. Investigators calculated a weighted HR that accounted for baseline differences.

- More than 15 days vs. less than 15 days: HR 0.98, 95% CI 0.76 to 1.26
- More than 30 days vs. less than 30 days: HR 0.95, 95% CI 0.73 to 1.23
- More than 60 days vs. less than 60 days: HR 0.84, 95% CI 0.61 to 1.15

CONCLUSIONS: The reviewers conclude that there is still insufficient evidence from RCTs to assess whether immediate or deferred ART initiation in 2 to 5 year old children most efficaciously provides clinical and immunological benefits.

QUALITY OF THE EVIDENCE: The reviewers used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to assess evidence quality. GRADE ranks the quality of evidence on four levels: "high," "moderate," "low" and "very low." Evidence from randomized controlled trials starts at "high," but can be downgraded for study limitations (risk of bias), inconsistency of results, indirectness of evidence, imprecision or for reporting bias. Evidence from observational studies starts at "low," but can be upgraded if the magnitude of treatment effect is very large, if there is a significant dose-response relation, or if all possible confounders would decrease the magnitude of an apparent treatment effect. Evidence from observational studies can also be downgraded. The reviewers found the quality of evidence to be low or very low for all outcomes. Across all outcomes in the trials, evidence quality was graded down for indirectness (when the reported results were not stratified with the outcomes for 24 to 59 month old children), imprecision (small sample size or low event rate) or both. They also graded down for risk of selection bias in the post-hoc sub-analysis of 24 to 59 month old children. In the observational study, reviewers graded down for risk of bias, indirectness and imprecision.

QUALITY OF THE REVIEW: This was a high quality systematic review. It meets every relevant criterion of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

IN CONTEXT: ART initiation in all children aged ≤5 years may facilitate scale-up of pediatric treatment in resource-limited settings with low ART coverage. It will nevertheless be critical in these contexts to prioritize ART to those children with a higher risk of mortality (e.g. infants aged under one year and children with advanced clinical and immunological disease).

PROGRAMMATIC IMPLICATIONS: In settings with wide access to CD4 monitoring, good ART coverage and adequate program retention, the authors suggest that CD4-guided ART initiation should not be viewed as sub-optimal standard of care. Pre-ART clinical follow up in children should be strengthened to ensure prompt recognition of disease progression as soon as this may occur. On the other hand, however, WHO, based on the same evidence, has recommended that all children <5 years old should begin ART regardless of WHO clinical stage of CD4 cell count or percentage. WHO classifies its recommendation as strong with moderate-quality evidence for infants diagnosed in the first year of life and conditional with very low-quality evidence for 1-to-4-year-old children.

Prevention of mother-to-child HIV transmission (PMTCT)


OBJECTIVE: To compare the efficacy and safety of infant nevirapine (NVP) among HIV-exposed breastfeeding infants compared to placebo for the prevention of postnatal HIV infection.

SETTING: South Africa, Tanzania, Uganda and Zimbabwe

STUDY DESIGN: Randomized controlled trial

POPULATION: Pregnant HIV-infected women who intended to breastfeed and their infants. Infants had to be HIV-uninfected (negative HIV DNA polymerase chain reaction test) at 7 days for age and have a birth weight >2000 grams.
INTERVENTION (PREDICTOR VARIABLE): NVP until cessation of breastfeeding vs. placebo.

MAIN OUTCOME MEASURES: Infant HIV infection at 18 months among those uninfected at 6 weeks; HIV-free and overall survival at 18 months; cumulative frequency and severity of adverse events.

METHODS: All infants received NVP 10 mg/mL suspension once daily for the first 6 weeks of life. Mothers were counseled to breastfeed exclusively for 6 months and then wean rapidly to breast milk substitutes and complementary foods. Infant randomization occurred at 6 weeks of age. Infants were stratified by maternal antiretroviral therapy (ART) at randomization. Infants were assessed for HIV infection at 3, 6, 9 and 12 months by HIV DNA and at 18 months by HIV antibody testing.

RESULTS: Between June 2008 and March 2010, 1,527 infants were randomized at age 6 weeks. Five infants (3 in NVP and 2 in placebo arm), who were later found to have had a positive HIV-1 DNA PCR at 6 weeks, were excluded from the analysis, leaving 1522 infants in the primary analyses: 759 infants for the primary analyses in the NVP arm and 763 infants in the placebo arm. Median maternal age was 27 years, and median infant birth weight was 3100 grams in both study product arms; 96% and 97% of women were WHO clinical stage I or II, and median CD4 count was 560 and 528 cells/µL in the NVP and placebo arms, respectively. Four hundred thirty nine (29%) mothers were receiving ART for their own health at the 6-week randomization visit, 220/752 (29%) on the NVP arm and 219/753 (29%) in the placebo arm. At 18 months there had been 26 infant deaths in the NVP arm and 30 in the placebo arm. There were 39 new infections after 6 weeks of age, 16 (2.2%, 95% confidence interval [CI] 1.1-3.3%) in the NVP arm and 23 (3.1%, 95% CI 1.9-4.4%) in the placebo arm (p=0.28). The 18-month cumulative HIV-free survival was similar in the two arms, as was the overall infant survival. Among the subset of mothers with CD4 counts of <350 cells/µL and not on ART, the 18-month cumulative postnatal infection rates were 8.9% (95% CI 2.6-15.1%) in the NVP arm and 9.6% (95% CI 2.3-17%) in the placebo arm (p=0.87). Among women with CD4 cell counts ≥350 cells/µL who were not otherwise eligible for ART, postnatal transmission risk at 18 months was 1.9% (95% CI 0.6-3.2%) in the NVP arm compared to 7.2% (95% CI 4.9-9.6%) in the placebo arm (p=0.12).

CONCLUSIONS: Despite an earlier finding of decreased risk of transmission between 6 weeks and 6 months in this study, this effect found no statistically significant difference at 18 months of age.

RISK OF BIAS: The risk of bias in this trial is low. Randomization was done according to computer-generated permuted block algorithms by site, with random block sizes. Participants and study personnel were masked to the assignment of NVP or placebo. There is no evidence of selective outcome reporting or other potential sources of bias.

IN CONTEXT: Previous studies have found that both extended infant and maternal prophylaxis are effective in reducing postnatal transmission among women who do not required ART for their own care. These findings of no effect are surprising given HPTN 046’s earlier finding of a significant reduction in transmission at 6 months of age.

PROGRAMMATIC IMPLICATIONS: The 2013 World Health Organization (WHO) treatment guidelines strongly recommend based on moderate-quality evidence that HIV-infected pregnant and breastfeeding women should start on ART and continue at least for the duration of risk of mother-to-child transmission (Option B). For programmatic and operational reasons, WHO also conditionally recommends based on low-quality evidence that all pregnant and breastfeeding women should start life-long ART (Option B+). In both of these recommendations, WHO recommends that babies should receive 6 weeks of nevirapine if breastfeeding or 4-6 weeks of nevirapine or zidovudine if formula feeding. Thus, the strategic approach of prolonged infant prophylaxis with rapid weaning at 6 months envisioned by HPTN 046 has been largely circumvented by Options B and B+. It is, however, very reassuring to note the low postnatal transmission rates (0.5% regardless of arm) reported in this paper among mothers who are on ART. Post-weaning transmission, however, remains a concern, since 7 of the 39 postnatal transmission events occurred after 6 months of age subsequent to at least one documented negative HIV DNA result after weaning; the mechanism for this remains unclear but may be due to unreported breastfeeding or other unexplained exposures.
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