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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.

NOTE ➤ We have developed a survey to evaluate our Lit Digest, in order to assess its impact and to learn from you about any ways in which it might be improved. We would be very grateful if you would go to this link to complete the survey: https://ucsf.co1.qualtrics.com/SE/?SID=SV_5bX8l0Mt33SFUKp

It should just take you a few minutes. Thank you very much in advance for helping us with this survey.

SUMMARIZED IN THIS EDITION:

Access to ART

ART MTCT and breastfeeding

Tuberculosis screening and isoniazid preventative therapy

Virological Failure

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Access to ART


OBJECTIVE: To determine if increased access to generic and free ART is correlated with higher rates of ART treatment initiation over time.

SETTING: Tertiary HIV referral center YR Gaitonde Centre for AIDS Research and Education (YRG CARE) in Chennai, India.

STUDY DESIGN: Retrospective double cohort study.

POPULATION: HIV-infected patients from YRG CARE and from the Johns Hopkins HIV Clinical Cohort (JHCC) in Baltimore, USA.

MAIN OUTCOME MEASURES: Time to initiation of ART.

METHODS: Two existing patient databases were utilized to conduct this retrospective cohort study and to conduct comparison calculations.

One database was comprised of HIV-infected patients receiving care at YRG CARE in Chennai, India between 1996-2007. Eligible patients were those who became eligible for ART during follow-up and were ART-naïve at the time of ART initiation. Patients were analyzed over three time periods: 1996-1999 (time period for which ART was available only for those who could pay out of pocket), 2000-2003 (time period during which ART was available at reduced costs) and 2004-2007 (time period during the Indian government’s free ART rollout). ART eligibility was defined as having a CD4 cell count <200, a Grade 3 or 4 event, or a CD4 cell count 201-350 and an opportunistic infection. ART regimen was defined as being on at least two drugs.

The other database was comprised of HIV-infected participants from the JHCC enrolled from 1996-2007. As with the YRG CARE cohort, eligible patients were those who became eligible for ART during follow-up and were ART-naïve at the time of ART initiation. In addition, ART eligibility was also defined as having a CD4 cell count <200 to keep consistency with the YRG CARE cohort. ART regimen was defined as being on at least three drugs.

Differences between the cohorts were tested using chi-square and Mann-Whitney tests. Differences within and between cohorts were tested using generalized gamma survival models to calculate the main outcome and predictors while controlling for confounders due to demographics, mode of HIV transmission and CD4 cell count at ART eligibility. Sensitivity analyses were also performed using a CD4 cell count eligibility of <350, using the same ART definition, and including patients who initiated ART within 60 days prior to enrollment.

RESULTS: The YRG CARE cohort had 5,726 patients eligible for inclusion, 77% of whom were male with an average age of 34 years. Over time patients were more often older and female and had lower CD4 cell counts at ART initiation. Compared to 2000-2003, time to ART initiation was 3.25 times longer in 1996-1999 (95% CI 2.53-4.17) and 0.73 times shorter in 2004-2007 (95% CI 0.63-0.83) in 2004-2007 compared to 2000-2003.

The JHCC cohort was 64% male with an average age of 39 years; participants in this cohort were more often female, less likely to have acquired HIV via sexual transmission and had higher CD4 cell counts at entry into the cohort compared to those in the YRG CARE cohort. Time to ART initiation was 4.90 times longer in the YRG CARE cohort compared to the JHCC cohort (95% CI 3.37-7.13) from 1996-1999 and 1.30 times longer (95% CI 0.97-1.75) from 2000-2003. Time to ART initiation was 0.31 times shorter (95% CI 0.22-0.44) in the YRG CARE cohort compared to the JHCC cohort from 2004-2007. Sensitivity analyses did not change conclusions from these results.

CONCLUSIONS: The authors concluded that ART took longer to initiate in the YRG CARE cohort compared to the JHCC cohort in the pre-generic time period but took a quarter of the time to initiate in the period of the Indian government’s free ART government rollout program.
RISK OF BIAS: The overall risk of bias in this retrospective double cohort study was moderate. Recall bias was reduced by obtaining data from existing patient records, but confounding bias when comparing the two cohorts to each other is a potential issue. Although the authors controlled in the statistical models for the known differences between the two cohorts, residual unmeasured confounding may remain and lead to potentially biased conclusions if the two groups were not actually similar to each other. The authors also point out in their discussion that the shorter time to ART initiation detected in the YRG CARE cohort compared to the JHCC cohort in the final time period might actually be due to the fact that YRG CARE cohort participants are allowed to begin ART at the moment they become eligible as opposed to the JHCC cohort participants often had to wait for at least a month to obtain insurance approval to initiate ART.

IN CONTEXT: This paper utilizes existing patient-level cohort data to demonstrate that generic and free ART programs can help decrease the time to ART initiation in developing country settings, such as India, and shows that ART can be initiated within time frames similar to those in the United States.

PROGRAMMATIC IMPLICATIONS: Access to generic and low-cost or free ART can lead to shorter time to ART initiation leading to individual and public health benefits. CD4 cell counts can be used to guide treatment decisions even in developing country settings as they become more widely available and economical.

ART MTCT and breastfeeding


OBJECTIVE: To determine whether a nucleoside reverse transcriptase inhibitor (NRTI)-based or a protease inhibitor (PI)-based ART regimen given to HIV-infected women during the third trimester of pregnancy improves maternal and infant health outcomes.

SETTING: Southern Botswana

STUDY DESIGN: Randomized control trial

POPULATION: HIV-infected pregnant women naïve to ART and choosing to breastfeed enrolled in the Mma Bana Study in southern Botswana.

MAIN OUTCOME MEASURES: Maternal death, time to maternal death, and time to death or CD4+ cell count below 200 cells/µL; child death, time to child death, and child HIV infection.

METHODS: Women were enrolled if they were HIV-infected, planning to breastfeed, and had CD4+ cell counts ≥ 200 cells/µL. Eligible participants were then randomized at 24-34 weeks of pregnancy to one of to two treatment arms. Arm 1 was an NRTI-based regimen consisting of abacavir (ABC), zidovudine (ZDV) and lamivudine (3TC), and Arm 2 was a PI-based regimen consisting of ritonavir-boosted lopinavir (LPV/r), ZDV and 3TC; both regimens were given twice daily until the first instance of weaning or being 6 months post-partum.

Data were also reported for an observational arm, which consisted of women entering the study at 18-34 weeks of pregnancy with CD4+ cell counts < 200 cells/µL or with an AIDS-defining illness; these women were provided with the nevirapine (NVP)-based standard of care which included NVP/ZDV twice-daily following a 2-week lead-in time of NVP once-daily. Mothers received ART until 6 months post-partum and were counseled to exclusively breastfeed their infants until 6 months of age. Infants in the study received NVP at birth and daily ZDV from birth to 4 weeks. Follow-up visits occurred monthly up to 7 months and then again at months 12, 15, 18 and 24 months.

Differences and factors associated with differences were tested using Poisson regression models using generalized estimating equations and with Kaplan-Meier estimators and log-rank tests.

RESULTS: The Mma Bana Study enrolled 730 participants, randomizing 285 to the NRTI-arm and 275 to the PI-arm; there were an additional 170 observational participants.
No significant difference was found between the randomized arms for maternal death (n=6 (2%) in the NRTI-arm vs. n=3 (1%) in the PI-arm) or number experiencing at least one grade 3 or 4 event (n=29 (10%) in the NRTI-arm vs. n=23 (8%) in the PI-arm). All but 1 maternal death occurred after stopping ART taken for PMTCT. For mothers time to death or CD4+ count below 200 was shorter in the NRTI-arm compared to the PI-arm (p=0.03).

A total of 8 children were found to be HIV-infected during 18 months follow-up; more children were infected in the NRTI-arm (n=6, 2.1%) than the PI-arm (n=1, 0.3%, p=0.123) and 1 child HIV-infected in the observation arm. No significant difference was found between the randomized arms for child death (n=13 (5%) in the NRTI-arm vs. n=15 (6%) in the PI-arm; p=0.71) nor between the randomized arms and the observational arm (p=0.69). The majority of child deaths occurred after weaning (22 out of 37 for the entire study population), and most of these occurred within 3 months of weaning.

No significant difference was found between randomized arms with regard to child HIV-free survival (p=0.74). Significant risk factors associated with child mortality included pre-term delivery (RR 3.43, 95% CI 1.51-7.82, p=0.003), child weight for age z-score (RR 1.64, 95% CI 1.20-2.24, p=0.002), child age (p=0.022) and child feeding (RR 4.07 for weaned within 3 months vs. still breastfeeding, RR 0.60 for weaned > 3 months prior vs. still breastfeeding, p=0.009).

CONCLUSIONS: The intervention was successful compared to the standard of care in achieving low rates of MTCT with no additional HIV transmission occurring after the 6-month intervention period, but the high number of maternal deaths upon stopping ART was concerning. For the primary outcome, maternal time to death or CD4+ cell count <200 cells/µL, the PI-arm was favored over the NRTI-arm; however it is important to note that although CD4+ cell counts increased faster in the PI-arm, viral load was suppressed faster in the NRTI-arm.

RISK OF BIAS: The overall risk of bias in this randomized clinical trial is low since participants were randomized to one of the two treatment arms and were extensively followed during the 24-month post-intervention period. One key limitation of the study is that it was underpowered to detect differences in regards to mortality, hospitalizations, or serious adverse events among mothers or their infants so conclusions based on these outcomes are limited.

IN CONTEXT: This paper utilizes a large randomized trial with 24 months of follow-up data to demonstrate that ART given to mothers in during the early part of their third trimester can reduce MTCT and suggests that PI-based regimens may be more effective than NRTI-based regimens.

PROGRAMMATIC IMPLICATIONS: Starting ART early in a pregnancy and achieving high levels of adherence to WHO infant feeding and weaning guidelines can significantly lower MTCT, and PI-based regimens may do so more effectively if available. This study supports recent updates to WHO guidelines which recommend treatment initiation at a CD4+ cell count of 500, but future studies should further investigate the long-term impacts maternal ART has on infant survival and health.

Tuberculosis screening and isoniazid preventative therapy


OBJECTIVE: To determine the effect of an intervention of tuberculosis (TB) screening, tuberculin testing and isoniazid preventative therapy on rates of TB and death.

SETTING: HIV clinics in Rio de Janeiro, Brazil.

STUDY DESIGN: Stepped-wedge cluster-randomized control trial.

POPULATION: HIV-infected patients attending one of 29 HIV clinics providing antiretroviral therap (ART) in Rio de Janeiro.

MAIN OUTCOME MEASURES: Incidence of TB and incidence of TB or death.
METHODS: All patients were included in the intervention if they had at least one clinic visit between September 2003 – September 2005 or had their first clinic visit from September 2005 – August 2009. Staff members were trained to administer a tuberculin skin test to HIV-infected patients with no previous TB diagnosis, treatment, or preventive therapy. Those testing positive were provided with preventive isoniazid 300 mg combined with pyridoxine 25 mg for 6 months. All staff at all clinics received training on the intervention. The order of clinic implementation was randomized and occurred in a staggered manner over the 5-year intervention period. The pre-intervention time served as a control comparison.

The primary data source was medical records, with additional data abstracted from surveillance databases. Differences and factors associated with differences in incidence were tested using Poisson regression models producing hazard ratios. Models were adjusted for age, sex, ART usage at baseline, and time-varying CD4 count and excluded those participants without a CD4 measurement. A secondary analysis was also conducted among “stayers”, defined as participants with consistent clinic follow-up.

RESULTS: The THRio cohort included 12,816 patients who were eligible for inclusion; 9,708 participants contributing to the control period and 10,752 to the intervention period. The median age was 37 years, 61% were men, and 60% were receiving ART at baseline.

Rates of positive tuberculin skin tests were significantly greater in the intervention period than in the control period (59/100 person-years (PY) vs. 19/100 PY, p<0.0001) and rates of initiation of isoniazid preventive therapy were higher as well (144/100 PY vs. 36/100 PY, p<0.0001).

Tuberculosis infection was lower in the intervention period compared to the control period, but this difference was only marginally significant in the adjusted analysis (HR 0.73, 95% CI 0.54-0.99, p=0.04). Tuberculosis infection or death was significantly lower in the intervention period compared to the control period in the unadjusted (HR 0.76, 95% CI 0.66-0.87, p<0.0001) and adjusted (HR 0.69, 95% CI 0.57-0.83, p<0.0001) analyses. In the secondary analysis including only “stayers” both outcomes of tuberculosis infection and the tuberculosis or death were even more significantly lower in the intervention period compared to the control period.

CONCLUSIONS: The authors concluded that the practical intervention of providing preventative isoniazid to HIV-infected patients with a positive tuberculin skin test can lower tuberculosis infection rates and death in contexts where ART is available and free.

RISK OF BIAS: The overall risk of bias in this stepped-wedge randomized trial is low since clinics were randomized to the order of intervention implementation. However, although the stepped-wedge design used is practical for this type of intervention, this study design is not fully protected from temporal trends that might have affected participants in the control or intervention period.

IN CONTEXT: This paper utilized the novel and practical stepped-wedge study design and randomized the order of clinic implementation to demonstrate that isoniazid preventive therapy for HIV-infected individuals with a positive tuberculin skin test can reduce tuberculosis and death even in the context of wide access to and uptake of ART. These findings are supported by other observational and randomized trial studies that have been conducted in various African and Asian countries.1-3

PROGRAMMATIC IMPLICATIONS: The provision of isoniazid preventive therapy is a relatively cheap and easy intervention to implement and can have significant personal and public health impacts. Rates of tuberculosis or death were even lower in the intervention period compared to the control period for those who were retained in care, emphasizing the critical importance of retention in care for HIV-infected individuals.

Virological Failure

OBJECTIVE: To provide 5-year follow-up data on the CHER study conducted to determine if early time-limited antiretroviral therapy (ART) or deferred ART lead to better outcomes for HIV-infected infants.

SETTING: Two clinics for HIV-infected children in South Africa, the Perinatal HIV Research Unit in Soweto and the Children’s Infectious Disease Clinical Research Unit in Cape Town.

STUDY DESIGN: Open-label randomized trial.

POPULATION: Asymptomatic HIV-infected infants ages 6-12 weeks old with CD4% ≥25% in South Africa.

MAIN OUTCOME MEASURES: Time to death/first-line ART failure, and virological failure. Multiple secondary outcomes were also included.

METHODS: Participants were randomized using permuted blocks stratified by clinical site to one of three treatment arms: deferred ART, ART begun immediately after diagnosis and given for 40 weeks and then stopped, or ART begun immediately after diagnosis and given for 96 weeks and then stopped. First-line ART was zidovudine (ZDV)/lamivudine (3TC)/ritonavir-boosted lopinavir (LPV/r); second-line ART was provided when necessary. Infants were followed-up monthly for the first 24 weeks, bi-monthly until 48 weeks and then every 12 weeks until the end of the 5-year study. Differences between the study arms were calculated using Kaplan-Meier plots, log-rank test and Cox proportional hazards models.

RESULTS: The CHER study enrolled a total of 377 HIV-infected infants (125 to the deferred ART arm, 126 to the 40-week ART arm, and 126 to the 96-week ART arm) and followed them for a median 4.8 years. Infants were a median age of 7.4 weeks with a median CD4% of 35%; 85% of infants were given ART for PMTCT, and 14.3% were breastfed. The median time between stopping ART and needing to restart it again was 33 weeks (95% CI 26-45) in the 40-week arm and 70 weeks (95% CI 35-109) in the 96-week arm.

Infants in both the 40-week arm and in the 96-week arm had significantly lower hazards of death or first-line ART failure (hazard ratio (HR) 0.59, 95% CI 0.38-0.93, p=0.023 and HR 0.47, 95% CI 0.29-0.76, p=0.002, respectively) compared to those in the deferred ART arm. The hazard of clinical progression was also significantly lower in both the 40-week arm (HR 0.53, 95% CI 0.34-0.83, p=0.005) and in the 96-week arm (HR 0.42, 95% CI 0.26-0.67, p=0.0003) compared to the deferred ART arm. In addition, the hazard of death or an HIV event was significantly lower in both the 40-week arm (HR 0.48, 95% CI 0.27-0.84, p=0.011) and the 96-week arm (HR 0.34, 95% CI 0.18-0.64, p=0.0009) compared to the deferred-ART arm.

CONCLUSIONS: The authors concluded that overall outcomes were better for infants in early time-limited 40- and 96-week ART arms compared to the deferred ART arm and that, between the two treatment arms, the 96-week ART arm outcomes were marginally better.

RISK OF BIAS: The overall risk of bias in this open-label randomized trial was low. The trial was open label and was not powered to detect a difference between the ART 40 week and ART 96 week arms but otherwise had no other bias issues of note.

IN CONTEXT: This paper is the first of its kind to utilize a randomized control trial of HIV-infected infants to demonstrate that time-limited ART leads to better clinically significant outcomes compared to deferred ART over 5 years of follow-up. In addition this study showed the feasibility of such an intervention and supports the use of LPV/r as part of first-line ART for infants.

PROGRAMMATIC IMPLICATIONS: The World Health Organization recommends that all HIV-infected infants and children less than 36 months of age begin ART at the time of diagnosis. These data provide direct evidence that early versus delayed therapy leads to lower mortality and HIV-related morbidity.
REFERENCES:

Solomon et al:

Shapiro et al:

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Cotton et al: