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Maternal 12-month response to antiretroviral therapy following prevention of mother-to-child transmission of HIV-1, Côte d'Ivoire, 2003-2006

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This study was reported in part at the 3rd IAS Conference on HIV pathogenesis and treatment in Rio de Janeiro, Brazil, 24-27 July 2005 (abstract Mo0a0203) and at the 14th Conference on Retroviruses and Opportunistic Infections, Los Angeles, USA, 25-28 February 2007 (late breaker abstract M1004).

ABSTRACT

Objective: To study the response to antiretroviral treatment (ART) of women exposed to single-dose nevirapine (sdNVP) and/or short-course (sc) zidovudine (ZDV) ± lamivudine (3TC) for the prevention of mother-to-child transmission of HIV (PMTCT).

Methods: In the MTCT-Plus program in Abidjan, all HIV-1 infected women who initiated ART with d4T/ZDV, 3TC, and NVP/Efavirenz were eligible. Exposed women had received sdNVP or sc(ZDV±3TC) + sdNVP during previous pregnancy. Genotypic resistance testing was performed at week-4 postpartum (PP). At 12 months after ART initiation virological failure was defined by a plasma HIV RNA >500 copies/ml.

Results: Among 247 ART-treated women, 109 (44%) were unexposed, 81 had received sc(ZDV+3TC)+sdNVP, 5 sc(ZDV+3TC), 50 scZDV+sdNVP and 2 sdNVP only. No ZDV mutation was detected (N=115); 11/73 (15.1%) 3TC-exposed women tested PP had 3TC resistance mutations. 3/69 (4.3%) women exposed to sc(ZDV+3TC)+sdNVP and 16/42 (38.1%) women exposed to scZDV+sdNVP had NVP resistance mutations. ART was initiated 21 months in median after PMTCT (median CD4 count of 188 cells/mm³). 12-month virological failure was identified in 42/219 (19.2%) women in whom data were available and was associated in multivariate analysis with poor adherence (adjusted odds ratio [aOR] 12.7, 95% [CI] 3.0-53.9), 3TC resistance mutations PP (aOR 6.9, CI 1.1-42.9) and a baseline CD4+ count <200/mm³ (aOR 0.3, CI 0.2-0.8). NVP resistance was not associated with virological failure (aOR 1.8, CI 0.5-6.5).

Conclusion: Our study identified poor adherence and 3TC resistance acquired after PMTCT intervention to be associated with virological failure in women initiating ART.

Introduction

Mother-to-child transmission (MTCT) is the most important source of human immunodeficiency virus type 1 (HIV) disease in children, with 1100 newly acquired infections every day in Africa (1, 2). Noticeable progress has been made to develop prevention of MTCT (PMTCT) programs based on clinical trial findings (3-10).

A single-dose of nevirapine (sdNVP) taken around delivery/birth by women and neonates is the most commonly used regimen used, with good relative efficacy (5, 9-11), ease of administration and low cost. This regimen has been endorsed by the World Health Organization (WHO) since 2001, but the most recent international guidelines recommend either the use of antiretroviral treatment (ART) with a combination of three drugs (usually including NVP) for pregnant women in need of treatment for their own health, or short-course zidovudine (scZDV) followed by sdNVP during labor and a seven-day postpartum (PP) short-course of ZDV and lamivudine (3TC) when ART is not yet indicated (1).

sdNVP induces viral resistance mutations to non-nucleoside reverse transcriptase inhibitors (NNRTI) which frequency varies between 15% and 67% at four to six weeks after delivery in women who received sdNVP alone or after scZDV for PMTCT (12-16). Thus, the relevant clinical question is whether these resistant viruses have an impact on future treatment options for the mother and the child when an NNRTI-based ART is subsequently initiated. Two publications in Thailand and Botswana found a poorer 6-month virological response to ART when the time interval between sdNVP exposure and ART initiation was <6 months (17, 18). Also, PP administration of ZDV+3TC for 3 or 7 days following sdNVP reduced the frequency of NNRTI viral resistance mutations from 33% to 1% in Côte d'Ivoire (14) and from 50% to 12% in South Africa (19) with unknown effects on ART response.

sc3TC is always used in combination with scZDV (8, 10) and leads to a moderate rate of 3TC resistance mutations estimated between 8%-12% after two months (14, 20); sc(ZDV+3TC)+sdNVP yielded a low perinatal HIV transmission rate of 4.7% in Côte d'Ivoire (10). Currently, there are no published data regarding the impact of PMTCT-acquired 3TC viral resistance mutations on the efficacy of subsequent ART, which usually includes 3TC in the first-line regimens in resource-limited settings (1).

We studied factors related to the 12-month immunological and virological responses to ART in women previously exposed to sdNVP and/or to sc(ZDV±3TC) for PMTCT.

Methods

Study design and setting

A prospective cohort study was conducted in Abidjan, Côte d'Ivoire between August 2003 and September 2006 among the women registered in the MTCT-Plus program, built upon existing PMTCT services and providing HIV-infected women, their partners and children, holistic family care with unrestricted access to ART (21).

Patients

HIV-infected women were included in this study if, i) they initiated ART according to the following eligibility criteria: WHO stage 2 (until December 2004) or stage 3 and lymphocytes T CD4+ (CD4+) count <350 cells/mm³, or stage 4 regardless of CD4+ count, or CD4+ count <200 cells/mm³, ii) had ≥ 1 prior pregnancy and iii) initiated an NNRTI-based ART before 30th September 2005. The unexposed women never received any treatment for PMTCT or for their own health (group 1). The exposed women received sdNVP for PMTCT, either alone during labor or following scZDV from 36 weeks of gestation (group 2) or sc (ZDV+3TC) initiated from 32 weeks and continued until three days PP (group 3). These PMTCT regimens of validated efficacy had been introduced sequentially in this population (10).

Ethical aspects

The exposed women were previously part of the French Agence Nationale de Recherches sur le SIDA (ANRS) 1201/1202 Ditrane Plus project. This study was approved by the Institutional Review Board of the ANRS and by the national ethics Committee of Côte d'Ivoire. All these women were subsequently enrolled in the MTCT-Plus program. As an HIV care and treatment program, the MTCT-Plus Initiative was exempted from review by the Columbia University IRB.

Inclusion and follow-up

Socio-demographic, clinical and biological characteristics were recorded at ART enrolment. During weekly follow-up visits for the first two months and then, every month, clinical signs and symptoms, drug intake and tolerance were collected. Patients were asked to self-report their pill intake during the previous seven days of the visits scheduled at month 6 and 12. Poor adherence was considered when the patients took only half, little or none of the pills during this time frame. CD4⁺ cell counts were measured by a dual-platform flow cytometry technique with an automated blood cell counter (MaxM, BeckmanCoulter, Miami, FL, USA) at the screening visit, then six and 12 months after ART initiation. For women with frozen samples routinely collected at the screening visit, at six and 12 months after ART initiation, plasma HIV-RNA levels were subsequently quantified, using the ANRS-approved real-time RT-PCR assay (22). The threshold of the assay was $2.7 \log_{10}$ (500) copies/ml using 200 μ l of plasma. At each visit, severe clinical events and laboratory abnormalities were recorded according to the internationally validated ANRS table for grading severity of adult adverse events (23).

HIV-1 genotypic resistance tests

A genotypic resistance test was performed in exposed women with available samples at week-4 PP. The HIV-1 reverse transcriptase (RT) genes were amplified from plasma HIV-RNA and sequenced (bulk sequencing) using the ANRS consensus technique (24). Drug resistance was defined according to the 2006 ANRS HIV-1 genotypic resistance interpretation algorithm (www.hivfrenchresistance.org). Resistance was subsequently investigated at 12 months post-ART initiation in those who had virological failure.

Outcomes

Three outcomes were considered after 12 months of NNRTI-based ART: 1) immunological failure defined by a >30% fall from CD4+ peak level on ART; 2) virological failure defined by plasma HIV-RNA >500 copies/ml; 3) overall failure defined by worsening of the WHO staging or the occurrence of death after ≥ 3 months on treatment or immunological failure or virological failure.

Statistical analysis

Group comparisons used Student's t-test, non-parametric Mann-Whitney U test or variance analysis for continuous variables, and Chi-2 test for trend or Fisher's exact test for categorical variables. Univariable then multivariable logistic regression analyses were performed with a stepwise descending selection procedure to identify factors associated with treatment failure. The main variables of interest, viral resistance to NVP or to 3TC at week 4 PP, were forced in all models, as well as CD4 count and WHO clinical stage at ART initiation (25). Adjusted odds ratios (aOR) and their 95% confidence interval (95% CI) are reported and p-values are two-sided. All analyses were performed in intent-to-treat with the SAS software version 9.1 (SAS Institute, Cary, NC, USA).

Results

Study population

From August 2003 to September 2005, 247 women initiated 3TC-containing-ART with either NVP or EFV (Figure 1). Their median age at ART initiation was 28 years (interquartile range [IQR]: 25-32) and median CD4+ cell count 188/mm³ (IQR: 126-264). Overall, 28 women (11.3%) were at WHO clinical stage 1, 110 (44.5%) at stage 2, 96 (38.9%) at stage 3 and 13 (5.3%) at stage 4. A total of 109 women (44.1%) had never been exposed to PMTCT (group 1) and 138 (55.9%) had been exposed. In the latter category, 50 had received scZDV+sdNVP and two sdNVP only (group 2); 81 had received sc(ZDV+3TC)+sdNVP and five sc(ZDV+3TC) only (group 3). The baseline characteristics are summarized in table 1 and were comparable between groups except that the women in group 2 were more advanced in their HIV disease based on WHO stage and had a higher median viral load.

Antiretroviral therapy

The first-line ART regimen was ZDV/3TC/NVP in 234 (95.1%) women, stavudine (d4T)/3TC/NVP in seven (2.8%) women, ZDV/3TC/EFV in five women (2.1%) and d4T/3TC/EFV in one woman. Cotrimoxazole was prescribed to 239 (97%) women. The median time interval between exposure to sdNVP and ART initiation was 21 months (IQR: 13-26); 28 months (IQR: 24-35) in group 2 and 15 months (IQR: 9-21) in group 3 ($p < 0.001$). The median duration of PMTCT exposure to 3TC was 54 days (IQR: 37-64) and the median time interval between exposure and ART initiation was 22 months (IQR: 10-16).

Viral resistance mutations after PMTCT

Among the 86 3TC-exposed women, 73 were tested for resistance mutations at 4 weeks PP and 11 (15.1%) [95% CI 7.8-25.4] had detectable 3TC resistance mutations. Among the 133 sdNVP-exposed women, 111 were tested at week 4 PP and 19 (17.1%) had detectable

NVP resistance mutations: 4.3% [95% CI 0.9-12.2] in group 3 and 38.1% [95% CI 23.6-54.4] in group 2. The list of overall resistance mutations is reported in table 2. Three women had both detectable 3TC and NVP resistance mutations. No resistance to ZDV was detected.

Follow-up of the patients

After 12 months of follow-up on ART, three women (1.2%) were lost to follow-up, seven (2.8%) stopped ART at their own request and nine (3.6%) died (figure 1). All the deaths occurred more than three months after ART initiation. Forty-six serious adverse events were reported among 39 women. This led to a switch from the NNRTI drug to a protease-inhibitor (PI) in 15 women (13 for grade 3 muco-cutaneous lesions, one for grade 4 liver toxicity and one for grade 4 neuropathy), or to abacavir due to grade 3 liver toxicity (n=1). Two women changed also the NNRTI drug to a PI owing to immunological failure. Overall, 88% of women declared to take almost or all the prescribed doses in the last seven days prior to the scheduled visits of month 6 and month 12 (p=0.83 between unexposed and exposed groups).

Clinical, immunological and virological failure

Among the 235 women alive with one-year follow-up, 13 (5.5%) presented a worsening of WHO stage but four occurred ≥ 3 months after initiating ART (figure 1).

Twenty-six women (11.1%) had immunological failure after 12 months on ART. No difference (trend test) was found by the presence or absence of NVP (p=0.08) or 3TC resistance mutations at week 4 PP (p=0.23) (figure 2). The median absolute CD4+ count increase was 238 cells/mm³ overall (IQR: 129-346): +230 cells mm³ (IQR: 124-342) in 19 women with NVP resistance mutations and +184 cells/mm³ (IQR: 129-264) in 11 women with 3TC resistance mutations.

After 12 months on ART, 219/235 (93.2%) women had a plasma sample available for HIV-RNA measurement. Among these women, 42 women (19.2%) had virological failure. Virological failure was not different (trend test) according to the presence or absence of NVP

resistance mutations at week 4 PP ($p=0.24$) (Figure 2). The frequency of virological failure was higher in women exposed to 3TC with viral resistance mutations at week 4 PP (50%) compared to women exposed to 3TC without viral resistance mutations (19.0%) and to women not exposed to 3TC (16.3%) ($p=0.04$) (Figure 2).

Viral resistance at 12 months

We realized 35 genotypic resistance tests among the 42 women with virological failure at 12 months. Among these, 18 (51.4%) had at least one viral resistance mutation (six exposed to sc(ZDV+3TC)+sdNVP, six to scZDV+sdNVP, one to sc(ZDV+3TC) and five not exposed). The relationship between the resistance profile at week 4PP in women who received PMTCT regimens and the occurrence of viral resistance mutations at 12 months on ART are summarized in Table 2. Neither NVP resistance nor 3TC resistance acquired after PMTCT exposure was associated with the occurrence of detectable viral resistance mutations at 12 months on ART (data not shown).

Factors associated with treatment failure

In multivariate analysis (Table 3), factors associated with virological failure were poor self-reported adherence (aOR 12.7, CI 3.0-53.9), 3TC resistance mutations at 4 weeks PP (aOR 6.9, 95% CI 1.1-42.9) and a baseline CD4+ count $<200/\text{mm}^3$ (aOR 0.3, CI 0.2-0.8), controlling for resistance mutations and exposure to NVP, maternal age, WHO clinical stage and hemoglobinemia at baseline. 3TC-exposed women who did not develop resistance mutations PP were not at increased risk of virological failure ($p=0.11$ in adjusted analysis). Exposure to sdNVP was not associated with virological failure (aOR 1.8, 95% CI 0.5-6.5 for NVP resistance mutations). Poor adherence was the only factor significantly associated in multivariable analysis with immunological failure (aOR 12.3, 95% CI 3.2-47.8) (Table 4) and with overall failure (aOR 25.89, 95% CI 7.40-90.61) (data not shown). Neither 3TC nor NVP resistance mutations were associated with immunological and overall failures at 12 months.

No interaction was found between the main variables of interest (viral resistance to NVP and to 3TC) for all models. Results remained unchanged in terms of relation between the three outcomes with adherence, CD4 count and NVP resistance/exposure, when restricting the analyses to groups 1 and 2 (data not shown).

Discussion

In this West African cohort where CRF02 virus is predominant (13, 14) , 11.0% of women presented immunological failure and 19.2% virological failure, 12 months after initiating ART containing 3TC and an NNRTI.

NVP resistance after sdNVP exposure was neither associated with virological nor immunological failure at 12 months of NNRTI- based ART in this population where median interval between PMTCT exposure and ART initiation was 21 months. This result is consistent with the data reported from Thailand (17), Botswana (18) and Zambia (26). In Thailand, no association was found regarding 6-month immunological and virological failure (>400 copies/mL) as well as with a threshold of 50 copies/mL when analysis was restricted to women for whom the interval between delivery and ART initiation was >12 months (17). In Botswana, there was also no difference in rate of virological failure (>400 copies/mL) between exposed and unexposed women when interval between delivery and ART initiation was ≥ 6 months (12.0% versus 7.8% respectively, $p=0.39$) (18). These findings confirm the hypothesis that NVP resistance mutations acquired after exposure to sdNVP at delivery decline over time (27) although minority resistant species can persist for up to two years (28). The clinical significance of these resistance profiles and their impact remain uncertain.

3TC resistance acquired through PMTCT was associated with a poorer 12-month virological response to subsequent 3TC-containing ART, but not to immunological failure although a trend was detected. Indeed, 3TC resistance mutations detected at week 4 PP in exposed women increased by six-fold the risk of virological failure and by two-fold the risk of immunological failure in comparison to unexposed women. The median duration of 3TC exposure was 54 days and the frequency of 3TC resistance mutations was 15.1%. It was

demonstrated in studies in France and in Côte d'Ivoire that the risk of viral resistance to 3TC is correlated with the duration of exposure (14, 29). This is the first time the association between the 3TC resistance-acquired with PMTCT was associated with virological failure on ART. Thus, a key question is the positioning of 3TC in the panel of PMTCT regimens and the frequency of occurrence of 3TC mutations when restricting the use of sc(ZDV+3TC)+sdNVP to HIV-infected women not eligible for ART. However, our team recently reported the long-term benefit at 18 months of sc(ZDV+3TC) starting at 32 weeks + sdNVP on the overall reduction of MTCT (30).

This study confirms that the addition of 3 days of PP (ZDV+3TC) to prepartum sc(ZDV+3TC) starting at 32 weeks plus sdNVP in intrapartum, compared to scZDV starting at 36 weeks in prepartum plus sdNVP in intrapartum, reduced the rate of NVP resistance from 38.1% to 4.3%. This finding confirms previous reports in Côte d'Ivoire and in South Africa where the rate of NVP resistance mutations fell respectively from 33.3% to 1.14 % and from 60% to 10-12% with sdNVP followed by 4 or 7 days of ZDV+3TC (14, 19).

We observed a median increase of 238 cells/mm³ of the CD4+ count at 12 months on ART. This observation is comparable to the data reported in Zambia with an increase of 201 cells at 12 months (26).

The consistent factor in predicting virological and immunological failure was poor adherence to ART. We used a self-reported technique to measure adherence; this method is used by 66% of African centers publishing on adherence and by 71% of North American centers (31). In a Uganda study, viral load ≥ 1000 copies/mL was associated with both pill count $< 95\%$ (aOR 10.6, 95% CI 2.5-45.7) and medication possession ratio of $< 95\%$ (aOR 9.4, 95% CI 3.4-26.2)

at 12 months (32). Of notice, the impact of adherence on virological failure after ART initiation was not documented in the three important studies of the relation between exposure to sdNVP and response to treatment (17, 18, 26). We suggest adherence be systematically investigated and reported in subsequent reports on this issue.

Three critiques can be formulated to our study:

First, we did not perform viral load analyses with ultra-sensitive assays as it was not routinely available for treatment monitoring in Abidjan. Lockman et al reported that there was no difference between exposed and unexposed groups when performing a viral load ultra-sensitive assay (18). Second, our study is slightly underpowered. Indeed, based on our findings, we would have needed at least 171 women in each group to detect any statistical difference in virological failure with 80% power between the women exposed to NNRTI or not. But the associations identified were consistent and coherent with previous reports. Finally, we did not perform an analysis stratified by time interval between PMTCT exposure and ART initiation because the median time interval was 21 months. However, it is likely that our study context reflects better the current field conditions of ART initiation in women PP than previous reports.

In practice, clinicians should prescribe seven days of ZDV+3TC in PP following sdNVP to reduce the emergence of NVP resistance mutations (1). The use of sc(ZDV+3TC) in partum is a concern from a viral resistance and future treatment perspective, based on our findings. This is likely to be explained by the joint effect of two drugs with low genetic barrier and the probable acquisition of minority variants resistant to NVP.

In conclusion, NNRTI-based ART initiated ≥ 1 year after PMTCT exposure including sdNVP remains a good therapeutic option at least for the first 12 months of treatment. This may be particularly relevant when such PMTCT regimens are restricted to women who do not need ART (33), with probably a greater chance of viral control and thus a lower risk of viral resistance.

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