# Abstracts from the current global literature

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## Safety, efficacy, and pharmacokinetics of TBR-652, a CCR5/CCR2 antagonist, in HIV-1–Infected, treatment-experienced, CCR5 antagonist–naive subjects

Lalezari J, Gathe J, Brinson C, Thompson M, Cohen C, Dejesus E, *et al*. Safety, Efficacy, and Pharmacokinetics of TBR-652, a CCR5/CCR2 Antagonist, in HIV-1–Infected, Treatment-Experienced, CCR5 Antagonist–Naive Subjects. J Acquir Immune Defic Syndr 2011;57:118-25.

*Objectives:* To determine the antiviral activity, pharmacokinetics, pharmacodynamics, safety and tolerability of several dose levels of oral TBR-652 monotherapy in HIV-1–infected, antiretroviral experienced, CCR5 antagonist-naive subjects. *Design:* Double-blind placebo-controlled study in the United States and Argentina. *Materials and Methods:* Subjects were randomized in a ratio of 4:1 per dose level to TBR-652 (25, 50, 75, 100, or 150 mg) or placebo, taken once daily for 10 days. Changes from baseline in HIV-1 RNA and CD4+ cell counts were measured through day 40 and for monocyte chemotactic protein-1 (MCP-1), high-sensitivity C-reactive protein (hs-CRP), and IL-6 at day 10. Pharmacokinetic data were analyzed using non-compartmental statistics. Laboratory and clinical adverse events (AEs) and electrocardiogram changes were recorded. *Results:* Maximum median reductions in HIV-1 RNA values for the 25, 50, 75, and 150 mg doses were −0.7, −1.6, −1.8, and −1.7 log10 copies per milliliter, respectively. All changes were significant. Median time to nadir was 10–11 days. Suppression persisted well into the post-treatment period. Mean MCP-1 increased significantly by day 10 in the 50-mg and 150-mg dose groups. Effects on CD4+ cell counts, hs-CRP, and IL-6 levels were negligible. TBR-652 was generally safe and well tolerated, with no withdrawals due to AEs. *Conclusions:* TBR-652 caused significant reductions in HIV-1 RNA at all doses. Significant increases in MCP-1 levels suggested a strong CCR2 blockade. TBR-652 was generally well tolerated, with no dose-limiting AEs. Pharmacodynamics indicate that TBR-652 warrants further investigation as an unboosted once-daily oral CCR5 antagonist with potentially important CCR2-mediated anti-inflammatory effects.

## Previous antiretroviral therapy for prevention of mother-to-child transmission of HIV does not hamper the initial response to PI-based multitherapy during subsequent pregnancy

Briand N, Mandelbrot L, Blanche S, Tubiana R, Faye A, Dollfus C, *et al*. Previous Antiretroviral Therapy for Prevention of Mother-to-Child Transmission of HIV Does not Hamper the Initial Response to PI-Based Multitherapy During Subsequent Pregnancy. J Acquir Immune Defic Syndr 2011;57:126-35.

*Background:* Limited data are available on the possible long-term negative effects of a short exposure to antiretroviral therapy (ART) for the prevention of mother-to-child transmission (PMTCT). *Objective:* To determine whether ART for PMTCT, discontinued after delivery, affects the virological response to highly active antiretroviral therapy (HAART) administered during subsequent pregnancies. *Materials and Methods:* All current pregnancies of HIV-1-infected women enrolled in the French Perinatal Cohort (ANRS CO-01 EPF) between 2005 and 2009 and not receiving ART at the time of conception were eligible. We studied the association between history of exposure to ART during a previous pregnancy and detectable viral load (VL) under multitherapy at current delivery (VL ≥50 copies/mL). *Results:* Among 1116 eligible women, 869 were ART-naive and 247 had received

**How to cite this article:**
Patel S, Chotaliya K, Marfatia YS. Abstracts from the current global literature. Indian J Sex Transm Dis 2011;32:129-33.

PMTCT during a previous pregnancy. Previous ART was protease inhibitor (PI)-based HAART in 48%, non-PI-based HAART in 4%, nucleoside reverse transcriptase inhibitor bitherapy in 19%, and zidovudine monotherapy in 29% of the women. At current pregnancy, women with or without prior exposure to ART had similar CD4 cell counts and VL before ART initiation. PI-based HAART was initiated in 90% of the women. VL was undetectable (<50 copies/mL) at delivery in 65% of the previously ART-naive women, 72% of women previously exposed to HAART, 62% previously exposed to bitherapy, and 67% previously exposed to monotherapy for prophylaxis ($P$ = 0.42). Detectable VL was not associated with previous exposure in multivariate analysis (adjusted OR for previous versus no previous exposure to ART: 0.92; 0.95% confidence interval: 0.59–1.44). *Conclusions:* Efficacy of PI-based combinations is not decreased in women previously exposed to various regimens of antiretroviral PMTCT.

## Tuberculosis risk before and after highly active antiretroviral therapy initiation: does HAART increase the short-term TB risk in a low incidence TB setting?

Pettit AC, Jenkins CA, Stinnette SE, Rebeiro PF, Blackwell RB, Raffanti SP, *et al*. Tuberculosis Risk Before and After Highly Active Antiretroviral Therapy Initiation: Does HAART Increase the Short-Term TB Risk in a Low Incidence TB Setting? J Acquir Immune Defic Syndr 2011 Aug 1;57(4):305-10

*Objective:* To evaluate the short-term and long-term effects of highly active antiretroviral therapy (HAART) on tuberculosis (TB) risk compared with the risk without HAART in a low-TB incidence setting. *Design:* An observational cohort study among HIV-infected persons in care at the Comprehensive Care Center (Nashville, TN) between January 1998 and December 2008. *Materials and Methods:* A marginal structural model was used to estimate the effect of HAART on short-term (≤180 days) and long-term (>180 days) TB risk, with $CD4^+$ lymphocyte count incorporated as a time-updated covariate. *Results:* Of 4534 HIV-infected patients, 34 developed TB (165 per 100,000 person-years; 20,581 person-years of follow-up). Seventeen cases occurred among persons not on HAART or >30 days after HAART discontinuation (212 per 100,000 person-years; 8019 person-years of follow-up). Seventeen occurred among persons on HAART (135 per 100,000 person-years; 12,562 person-years of follow-up), 10 in the first 180 days (402 per 100,000 person-years; 2489 person-years of follow-up), and seven after more than 180 days (69 per 100,000 person-years; 10,073 person-years of follow-up). After adjusting for the most recent $CD4^+$ lymphocyte count, the risk of TB in the first 180 days of HAART exposure relative to no HAART was 0.68 (0.14–3.22, $P$ = 0.63). *Conclusions:* In this low-TB incidence setting, the TB rate in the first 180 days of HAART was almost twice as high as persons not on HAART. However, after adjusting for most recent $CD4^+$ count, there was no significant difference in TB risk between these two groups. This suggests that low recent $CD4^+$ lymphocyte count influences TB risk during the first 180 days of HAART.

## Use of zidovudine-sparing HAART in pregnant HIV-infected women in Europe: 2000–2009

Tariq S, Townsend CL, Cortina-Borja M, Duong T, Elford J, Thorne C, *et al*. Use of Zidovudine-Sparing HAART in Pregnant HIV-Infected Women in Europe: 2000–2009. J Acquir Immune Defic Syndr 2011;57(4): 326-33.2011.

*Background:* Increasing numbers of women in resource-rich settings are prescribed zidovudine (ZDV)-sparing highly active antiretroviral therapy (HAART) in pregnancy. We compare ZDV-sparing with ZDV-containing HAART in relation to maternal viral load at delivery, mother-to-child transmission (MTCT) of HIV, and congenital abnormality. *Materials and Methods:* This is an analysis of data from the National Study of HIV in Pregnancy and Childhood and the European Collaborative Study. Data on 7573 singleton births to diagnosed HIV-infected women between January 2000 and June 2009 were analyzed. Logistic regression models were fitted to estimate adjusted odds ratios (AORs). *Results:* Overall, 15.8% (1199 of 7573) of women received ZDV-sparing HAART, with increasing use between 2000 and 2009 ($P$ < 0.001). Nearly one-fifth (18.4%) of the women receiving ZDV-sparing HAART in pregnancy had a detectable viral load at delivery compared with 28.6% of the women on ZDV-containing HAART [AOR 0.90; 95% confidence interval (CI): 0.72–1.14, $P$ = 0.4]. MTCT rates were 0.8% and 0.9% in the ZDV-sparing and ZDV-containing groups, respectively (AOR 1.81; 95% CI: 0.77–4.26, $P$ = 0.2). The congenital abnormality rate was the same in both groups (2.7%, AOR 0.98; 95% CI: 0.66–1.45, $P$ = 0.9), with no significant difference between the groups in a subanalysis of pregnancies with first trimester HAART exposure (AOR 0.79; 95% CI: 0.48–1.30, $P$ = 0.4). *Conclusions:* We found no difference in the risk of detectable viral load at delivery, MTCT, or congenital abnormality when comparing ZDV-sparing with ZDV-containing HAART. With increasing use of ZDV-sparing HAART, continued monitoring of

pregnancy outcomes and long-term consequences of *in utero* exposure to these drugs is required.

## Post-exposure prophylaxis following sexual exposure to HIV: A seven-year retrospective analysis in a regional centre

McCarty EJ, Quah S, Maw R, Dinsmore WW, Emerson CR. Post-exposure prophylaxis following sexual exposure to HIV: A seven-year retrospective analysis in a regional centre. Int J STD AIDS 2011;22:407-8.

An audit of 72 patients presenting for post-exposure prophylaxis following sexual exposure (PEPSE) to HIV (68 genitourinary medicine and four accident and emergency) was conducted from 2003 to 2009. The principal indications for PEPSE included 27 (38%) unprotected intercourse (15/27 vaginal and 12/27 anal) with a known HIV-positive partner, 20 (28%) unprotected receptive anal sex with male partner of unknown status, 17 (24%) following sexual assault, and three (4%) unprotected sex with a partner from an endemic country. Of those who commenced PEPSE, 92% did so within the recommended 72 h. Concurrent sexually transmitted infection (STI) was diagnosed in 8.3% patients (6.9% non-gonococcal urethritis and 1.4% rectal chlamydia). Fifty (69%) patients attended for follow-up and only 8% of these did not complete treatment. Twenty-five (35%) patients attended for repeat serology at 3 months and 18 (25%) at 6 months. All the patients followed-up remained HIV-negative.

## Post-HAART outcomes in pediatric populations: comparison of resource-limited and developed countries

Peacock-Villada E, Richardson BA, John-Stewart GC. Post-HAART outcomes in pediatric populations: Comparison of resource-limited and developed countries. Pediatrics 2011;127:e423-41.

*Context:* No formal comparison has been made between the pediatric post-highly active antiretroviral therapy (HAART) outcomes of resource-limited and developed countries. *Objective:* To systematically quantify and compare major baseline characteristics and clinical end points after HAART between resource-limited and developed settings. *Materials and Methods:* Published articles and abstracts (International AIDS Society 2009, Conference on Retroviruses and Opportunistic Infections 2010) were examined from inception (first available publication for each search engine) to March 2010. Publications that contained data on post-HAART mortality, weight-for-age z score (WAZ), CD4 count, or viral load (VL) changes in pediatric populations were reviewed. Selected studies met the following criteria: (1) patients were younger than 21 years, (2) HAART was given (≥3 antiretroviral medications), and (3) there were >20 patients. Data were extracted for baseline age, CD4 count, VL, WAZ and mortality, CD4, and virologic suppression over time. Studies were categorized as having been performed in a resource-limited country (RLC) or developed country (DC) on the basis of the United Nations designation. Mean percentage of deaths per cohort and deaths per 100 child-years, baseline CD4 count, VL, WAZ, and age were calculated for RLCs and DCs and compared by using independent samples t-tests. *Results:* Forty RLC and 28 DC publications were selected ($N$=17 875 RLCs; $N$=1835 DC). Mean percentage of deaths per cohort and mean deaths per 100 child-years after HAART were significantly higher in RLCs than in DCs (7.6 vs 1.6, $P$<0.001, and 8.0 vs 0.9, $P$<0.001, respectively). Mean baseline CD4% was 12% in RLCs and 23% in DCs ($P$=0.01). Mean baseline VLs were 5.5 vs 4.7 log(10) copies per mL in RLCs versus DCs ($P$<0.001). *Conclusions:* Baseline CD4% and VL differ markedly between DCs and RLCs, as does mortality after pediatric HAART. Earlier diagnosis and treatment of pediatric HIV in RLCs would be expected to result in better HAART outcomes.

## Interventions for the prevention and management of oropharyngeal candidiasis associated with HIV infection in adults and children

Pienaar ED, Young T, Holmes H. Interventions for the prevention and management of oropharyngeal candidiasis associated with HIV infection in adults and children. Cochrane Database Syst Rev 2010;11:CD003940.

*Background:* Oral candidiasis associated with human immunodeficiency virus (HIV) infection occurs commonly and recurs frequently, often presenting as an initial manifestation of the disease. Left untreated, these lesions contribute considerably to the morbidity associated with HIV infection. Interventions aimed at preventing and treating HIV-associated oral candidal lesions form an integral component of maintaining the quality of life for affected individuals. *Objectives:* To determine the effects of any intervention in preventing or treating OC in children and adults with HIV infection. *Selection criteria:* Randomised controlled trials (RCTs) of palliative, preventative, or curative therapy were considered, irrespective of whether the control group received a placebo. Participants were HIV-positive adults and children. *Results:* The review included

33 studies ($n$=3445): 22 assessing treatment and 11 assessing prevention of OC. Six studies were performed in developing countries, 16 in the United States of America and the remainder in Europe. Treatment was assessed in the majority of trials looking at both clinical and mycological cures. Compared with nystatin, fluconazole favored clinical cure in adults. There was no difference with regard to clinical cure between fluconazole compared with ketoconazole, itraconazole, clotrimazole, or posaconazole. Two trials compared different dosages of fluconazole with no difference in clinical cure. When compared with clotrimazole, both fluconazole and itraconazole proved to be better for mycological cure. Both gentian violet and ketoconazole were superior to nystatin in bringing about clinical cure. Comparing continuous fluconazole treatment with intermittent treatment, there was no significant difference between the two treatment arms. *Conclusions:* Because of there being only one study in children, it is not possible to make recommendations for the treatment or prevention of OC in children. Among adults, there were few studies per comparison. Because of insufficient evidence, no conclusion could be made about the effectiveness of clotrimazole, nystatin, amphotericin B, itraconazole, or ketoconazole with regard to OC prophylaxis. In comparison with placebo, fluconazole is an effective preventative intervention. However, the potential for resistant Candida organisms to develop, as well as the cost of prophylaxis, might impact the feasibility of implementation. No studies were found comparing fluconazole with other interventions. The direction of findings suggests that ketoconazole, fluconazole, itraconazole, and clotrimazole improved the treatment outcomes. It is encouraging that low-cost alternatives are being tested, but more research needs to be done in this area and on interventions like gentian violet and other less-expensive anti-fungal drugs to treat OC. There is also a strong need for more research to be done on the treatment and prevention of OC in children as it is reported that OC is the most frequent fungal infection in children and adolescents who are HIV positive. More research on the effectiveness of less-expensive interventions also needs to be done in resource-poor settings.

## Antiretroviral treatment reverses HIV-associated anemia in rural Tanzania

Johannessen A, Naman E, Gundersen SG, Bruun JN. Antiretroviral treatment reverses HIV-associated anemia in rural Tanzania. BMC Infect Dis 2011;11:190.

*Background:* HIV-associated anemia is common, and is associated with poor prognosis. However, its response to antiretroviral treatment (ART) in rural Africa is poorly understood. *Methods*: HIV-infected adults (≥15 years) who enrolled in HIV care at Haydom Lutheran Hospital in northern Tanzania were included in the study. The effect of ART (zidovudine/stavudine+lamivudine+efavirenz/nevirapine) on HIV-associated anemia was studied in a subset of patients who were anemic at the time they started ART and had a follow-up hemoglobin measurement 12 months later. Pregnant women were excluded from the study, as were women who had given birth within the past 6 weeks. Anemia was defined as hemoglobin <12 g/dL in women and <13 g/dL in men. We applied paired sample T-tests to compare hemoglobin levels before and 1 year after ART initiation, and logistic regression models to identify predictors of persistent anemia. *Results:* At enrollment, mean hemoglobin was 10.3 g/dL, and 649 of 838 patients (77.4%) were anemic. Of the anemic patients, 254 (39.1%) had microcytosis and hypochromia. Among 102 patients who were anemic at ART initiation and had a follow-up hemoglobin measurement after 12 months, the mean hemoglobin increased by 2.5 g/dL ($P$<0.001); however, 39 patients (38.2%) were still anemic after 12 months of ART. Independent predictors of persistent anemia were mean cell volume in the lower quartile (<76.0 fL; Odds Ratio [OR] 4.34; 95% confidence interval [CI] 1.22–15.5) and a zidovudine-containing initial regimen (OR 2.91; 95% CI 1.03–8.19). *Conclusions:* Most patients had anemia at enrollment, of whom nearly 40% had microcytosis and hypochromia suggestive of iron deficiency. The mean hemoglobin increased significantly in patients who received ART, but one-third were still anemic 12 months after ART initiation, indicating that additional interventions to treat HIV-associated anemia in rural Africa might be warranted, particularly in patients with microcytosis and those treated with zidovudine.

## Impact of targeted interventions on Heterosexual Transmission of HIV in India

Kumar R, Mehendale SM, Panda S, Venkatesh S, Lakshmi P, Kaur M, *et al*. Impact of Targeted Interventions on Heterosexual Transmission of HIV in India. BMC Public Health 2011;11:549.

*Background:* Targeted interventions (TIs) have been a major strategy for HIV prevention in India. We evaluated the impact of TIs on HIV prevalence in high HIV prevalence southern states (Tamil Nadu, Karnataka, Andhra Pradesh and Maharashtra). *Materials and Methods:* A quasi-experimental approach was used to retrospectively compare changes in HIV prevalence according to the intensity

of targeted intervention implementation. Condom gap (number of condoms required minus condoms supplied by TIs) was used as an indicator of TI intensity. Annual average number of commercial sex acts per female sex worker (FSW) reported in the Behavioral Surveillance Survey was multiplied by the estimated number of FSWs in each district to calculate the annual requirement of condoms in the district. Data of condoms supplied by TIs from 1995 to 2008 was obtained from program records. Districts in each state were ranked into quartiles based on the TI intensity. Primary data of HIV Sentinel Surveillance was analyzed to calculate HIV prevalence reductions in each successive year taking 2001 as the reference year according to the quartiles of TI intensity districts using generalized linear model with logit link and binomial distribution after adjusting for age, education, and place of residence (urban or rural). *Results:* In the high HIV prevalence southern states, the number of TI projects for FSWs increased from 5 to 310 between 1995 and 2008. In high TI intensity quartile districts ($n$=30), 186 condoms per FSW/year were distributed through TIs as compared with 45 condoms/FSW/year in the low TI intensity districts ($n$=29). Behavioral surveillance indicated significant rise in condom use from 2001 to 2009. Among FSWs, consistent condom use with last paying clients increased from 58.6% to 83.7% ($P$<0.001), and among men of reproductive age, the condom use during sex with non-regular partner increased from 51.7% to 68.6% ($P$<0.001). A significant decline in HIV and syphilis prevalence has occurred in high-prevalence southern states among FSWs and young antenatal women. Among young (15–24 years) antenatal clinic attendees, a significant decline was observed in HIV prevalence from 2001 to 2008 (OR=0.42, 95% CI 0.28–0.62) in high TI intensity districts whereas in low TI intensity districts, the change was not significant (OR=1.01, 95% CI 0.67–1.5). *Conclusion:* Targeted interventions are associated with HIV prevalence decline. Key Words: HIV, Impact, Evaluation, Condoms, Targeted Interventions, India.

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**DOI:** 10.4103/0253-7184.85426