nebulized albuterol, ipratropium did not have a significant impact on PEFR, length of stay in the emergency department, or hospitalization rate. However, an insufficient number of patients were enrolled in this study to demonstrate small differences in outcomes, if they existed. Larger clinical trials are needed to further investigate this widely used therapy.

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Continuous Terbinafine Versus Intermittent Itraconazole for Toenail Onychomycosis

Evans EG, Sigurgeirsson B. Double-blind, randomised study of continuous terbinafine compared with intermittent itraconazole in treatment of toenail onychomycosis. BMJ 1999; 318:1031-5.

Clinical question **How do continuous terbinafine and intermittent itraconazole compare in efficacy and safety for the treatment of toenail onychomycosis?**

Background Onychomycosis is one of the most common nail diseases, and one of the few that is treatable. Commonly used systemic therapies include terbinafine, which is primarily fungicidal, and itraconazole, which is primarily fungistatic. Because itraconazole persists in therapeutic concentrations after discontinuation of treatment, it is commonly prescribed in a pulse-like manner. This study is the first large-scale double-blind comparison of continuous terbinafine and intermittent itraconazole.

Population studied The study included men and women aged 18 to 75 years from 35 centers in 6 European countries with the clinical diagnosis of onychomycosis. All had involvement of the great toe confirmed by a positive mycologic culture and positive KOH microscopy. Patients were excluded for use of systemic antifungals in the previous 12 months or topical antifungals in the previous 4 weeks, and for drugs or conditions known to interact with the effectiveness or safety of the study drugs.

Study design and validity This was a prospective randomized double-blind multicenter parallel group study lasting 72 weeks that was funded by Novartis, the manufacturer of terbinafine. Patients were randomly allocated to 1 of 4 groups: T_{12}, terbinafine 250 mg (1 tablet) once a day for 12 weeks; T_{16}, terbinafine 250 mg (1 tablet) once a day for 16 weeks; I_3, itraconazole 400 mg (4 capsules) each day for 1 week in every 4 weeks for a 12-week period; and I_4, itraconazole 400 mg (4 capsules) each day for 1 week in every 4 weeks for a 16-week period. Placebo tablets and capsules were used "double dummy" to ensure that all patients took 1 tablet a day for 16 weeks plus 4 capsules a day during the 1st, 5th, 9th, and 13th weeks. The 4 groups were similar regarding mean age, percentage of women, race, number of infected toenails, species of dermatophyte causing infection, proportion of target nail involved, and duration of current episode of infection. Compliance criteria were appropriate and well defined. Results were analyzed on an intention-to-treat basis.

The lack of a control group was a primary limitation, and the reported results contained minimal statistical data. Incomplete explanation was provided for discrepancies between the number of patients used in the tabulation of the final results and the number of patients who completed the study. And treatment other than experimental medication was not delineated. For example, did patients file nails, receive any other confounding medications once the study began, or change hygiene habits? Finally, the evaluation of drug safety did not describe the methods used to collect complaints of side effects and lacked laboratory data to further support safety, such as follow-up monitoring of the initially gathered liver function tests and creatinine levels.

Outcomes measured The primary disease-oriented outcome was mycologic cure at 72 weeks, defined as negative culture and KOH microscopy. The primary patient-oriented outcomes were clinical cure (100% toenail clearing) at 72 weeks, complete cure (mycologic and clinical cure), and clinical effectiveness (mycologic cure and at least 5 mm of new clear toenail growth). Patients and physicians made global assessments of the perceived condition of all affected at weeks 12 and 72; the amount of improvement was rated on a scale from poor to excellent.

Results Of the 496 patients randomized to 1 of 4 treatment groups, 409 completed the study. The authors accounted for all withdrawals. Mycologic cure rates were: T_{12} = 76% (81 of 107); T_{16} = 81% (80 of 99); I_3 = 38% (41 of 107); and I_4 = 49% (53 of 108); $P < .001$. In all other outcomes measured, terbinafine was also shown to be significantly superior (range = $P < .001$ to $P \leq .004$). However, the clinical cure rate was much lower than the mycologic cure rate in all treatment groups: T_{12}, 54% (59 of 110); T_{16}, 60% (59 of 98); I_3, 32% (34 of 107); and I_4, 32% (35 of 109). Therefore,

the percentage of complete cure, a combination of both mycologic and clinical cure, was also lower: T_{12}, 46% (49 of 107); T_{16}, 55% (54 of 98); I_3, 23% (25 of 107); and I_4, 26% (28 of 108). Only 6.8% (34 of 496) withdrew for adverse events, and those patients were evenly distributed among the 4 groups.

Recommendations for clinical practice **Continuous terbinafine is more effective than intermittent itraconazole at achieving the goal of clear toenail growth. There was 1 additional clinical cure at 72 weeks for every 4.3 patients treated for 12 weeks with continuous terbinafine. However, there are additional important considerations for the physician when determining whether to initiate any medical therapy for toenail onychomycosis. These include the low rate of complete cure, a significant rate of patient withdrawal because of adverse events, the high cost of treatment, any concurrent patient conditions (human immunodeficiency virus or acquired immunodeficiency syndrome, diabetes, immunocompromise, and so forth), and a recurrence rate of at least 22%[1] at 3 years after successful initial treatment.**

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Elective Cesarean Delivery to Prevent Vertical Transmission of HIV

The International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1: a meta-analysis of 15 prospective cohort studies. N Eng J Med 1999; 340:977-87.

Clinical question **Does elective cesarean delivery reduce the risk of vertical transmission of human immunodeficiency virus type 1 (HIV-1)?**

Background Almost 7000 HIV-infected women give birth each year in the United States, but the optimal strategy to reduce transmission to children remains unclear. This meta-analysis reviews cohort studies addressing whether cesarean delivery prevents HIV transmission.

Population studied This is a meta-analysis of data on 8533 mother-child pairs from 15 North American and European prospective cohort studies. Thirteen percent of the mothers had advanced disease, defined as a prior diagnosis of acquired immunodeficiency syndrome or low CD4+ cell count, and 17% of the infants weighed less than 2500 g. Only 17% of the mothers received antiretroviral therapy, and no information was available about viral load. Thus, although the patients seem similar to those cared for by family physicians and obstetricians in the United States, an important difference is the low intensity of treatment of HIV-positive mothers in the study subjects. Monotherapy during pregnancy is now standard, and combination therapies are increasingly frequent.

Study design and validity This is a well-designed meta-analysis. Eligible studies were identified by a MEDLINE search and discussion with colleagues. The primary analysis was restricted to prospective cohort studies including at least 100 mother-child pairs enrolled before 1997 for which the route and circumstances of delivery and infant HIV infection status were known. Four categories of deliveries were distinguished: elective cesarean , nonelective cesarean, instrumental vaginal, and noninstrumental vaginal. Cesarean deliveries were considered elective if performed before the rupture of membranes and onset of labor. There was no evidence of heterogeneity among studies. Multivariate analysis was used to control for receipt of antiretroviral therapy, advanced maternal disease, and low birth weight. The weaknesses of the study are minor and include a poor description of the search criteria and study review process and the lack of sufficient control for confounding for viral load.

Outcomes measured The primary outcome measure was the rate of HIV-1 infection in infants. Clinically important outcomes of patient satisfaction, cost, and postdelivery complications were not addressed.

Results Elective cesarean delivery was associated with a much lower risk of vertical HIV transmission (odds ratio = 0.43; 95% confidence interval, 0.33 - 0.56); adjustment for covariates did not change this result. Among women who did not receive antiretroviral therapy, the rate of transmission was 10.4% for elective cesarean compared with 19.0% for other modes of delivery. With antiretroviral therapy, the transmission rate was only 2.0% for elective cesarean compared with 7.3% for other modes. The protective effect of elective cesarean delivery remained even when there was a short period between the rupture of membranes and delivery, suggesting that either the rupture of membranes or labor itself increases the risk of HIV transmission. If estimates for women receiving antiretroviral therapy are accurate, 1 case of vertical transmission of HIV would be prevented for every 19 women undergoing cesarean delivery before the onset of labor or rupture of membranes.