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ESCMID Executive Office
P.O. Box 214
CH-4010 Basel
Switzerland

Phone +41 61 508 01 53
info@escmid.org
www.escmid.org

Literature
Year in Infectious diseases

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Hydrocortisone plus Fludrocortisone for Adults with Septic Shock.

Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot JP, Siami S, Cariou A, Forceville X, Schwebel C, Martin C, Timsit JF, Misset B, Ali Benali M, Colin G, Souweine B, Asehnoune K, Mercier E, Chimot L, Charpentier C, François B, Boulain T, Petitpas F, Constantin JM, Dhonneur G, Baudin F, Combes A, Bohé J, Loriferne JF, Amathieu R, Cook F, Slama M, Leroy O, Capellier G, Dargent A, Hissem T, Maxime V, Bellissant E; CRICS-TRIGGERSEP Network.

BACKGROUND: Septic shock is characterized by dysregulation of the host response to infection, with circulatory, cellular, and metabolic abnormalities. We hypothesized that therapy with hydrocortisone plus fludrocortisone or with drotrecogin alfa (activated), which can modulate the host response, would improve the clinical outcomes of patients with septic shock.

METHODS: In this multicenter, double-blind, randomized trial with a 2-by-2 factorial design, we evaluated the effect of hydrocortisone-plus-fludrocortisone therapy, drotrecogin alfa (activated), the combination of the three drugs, or their respective placebos. The primary outcome was 90-day all-cause mortality. Secondary outcomes included mortality at intensive care unit (ICU) discharge and hospital discharge and at day 28 and day 180 and the number of days alive and free of vasopressors, mechanical ventilation, or organ failure. After drotrecogin alfa (activated) was withdrawn from the market, the trial continued with a two-group parallel design. The analysis compared patients who received hydrocortisone plus fludrocortisone with those who did not (placebo group).

RESULTS: Among the 1241 patients included in the trial, the 90-day mortality was 43.0% (264 of 614 patients) in the hydrocortisone-plus-fludrocortisone group and 49.1% (308 of 627 patients) in the placebo group (P=0.03). The relative risk of death in the hydrocortisone-plus-fludrocortisone group was 0.88 (95% confidence interval, 0.78 to 0.99). Mortality was significantly lower in the hydrocortisone-plus-fludrocortisone group than in the placebo group at ICU discharge (35.4% vs. 41.0%, P=0.04), hospital discharge (39.0% vs. 45.3%, P=0.02), and day 180 (46.6% vs. 52.5%, P=0.04) but not at day 28 (33.7% and 38.9%, respectively; P=0.06). The number of vasopressor-free days to day 28 was significantly higher in the hydrocortisone-plus-fludrocortisone group than in the placebo group (17 vs. 15 days, P<0.001), as was the number of organ-failure-free days (14 vs. 12 days, P=0.003). The number of ventilator-free days was similar in the two groups (11 days in the hydrocortisone-plus-fludrocortisone group and 10 in the placebo group, P=0.07). The rate of serious adverse events did not differ significantly between the two groups, but hyperglycemia was more common in hydrocortisone-plus-fludrocortisone group.

CONCLUSIONS: In this trial involving patients with septic shock, 90-day all-cause mortality was lower among those who received hydrocortisone plus fludrocortisone than among those who received placebo.

PMID: 29490185

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Adjunctive Glucocorticoid Therapy in Patients with Septic Shock.

Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, Billot L, Correa M, Glass P, Harward M, Joyce C, Li Q, McArthur C, Perner A, Rhodes A, Thompson K, Webb S, Myburgh J; ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group.

BACKGROUND: Whether hydrocortisone reduces mortality among patients with septic shock is unclear.

METHODS: We randomly assigned patients with septic shock who were undergoing mechanical ventilation to receive hydrocortisone (at a dose of 200 mg per day) or placebo for 7 days or until death or discharge from the intensive care unit (ICU), whichever came first. The primary outcome was death from any cause at 90 days.

RESULTS: From March 2013 through April 2017, a total of 3800 patients underwent randomization. Status with respect to the primary outcome was ascertained in 3658 patients (1832 of whom had been assigned to the hydrocortisone group and 1826 to the placebo group). At 90 days, 511 patients (27.9%) in the hydrocortisone group and 526 (28.8%) in the placebo group had died (odds ratio, 0.95; 95% confidence interval [CI], 0.82 to 1.10; P=0.50). The effect of the trial regimen was similar in six prespecified subgroups. Patients who had been assigned to receive hydrocortisone had faster resolution of shock than those assigned to the placebo group (median duration, 3 days [interquartile range, 2 to 5] vs. 4 days [interquartile range, 2 to 9]; hazard ratio, 1.32; 95% CI, 1.23 to 1.41; P<0.001). Patients in the hydrocortisone group had a shorter duration of the initial episode of mechanical ventilation than those in the placebo group (median, 6 days [interquartile range, 3 to 18] vs. 7 days [interquartile range, 3 to 24]; hazard ratio, 1.13; 95% CI, 1.05 to 1.22; P<0.001), but taking into account episodes of recurrence of ventilation, there were no significant differences in the number of days alive and free from mechanical ventilation. Fewer patients in the hydrocortisone group than in the placebo group received a blood transfusion (37.0% vs. 41.7%; odds ratio, 0.82; 95% CI, 0.72 to 0.94; P=0.004). There were no significant between-group differences with respect to mortality at 28 days, the rate of recurrence of shock, the number of days alive and out of the ICU, the number of days alive and out of the hospital, the recurrence of mechanical ventilation, the rate of renal-replacement therapy, and the incidence of new-onset bacteremia or fungemia.

CONCLUSIONS: Among patients with septic shock undergoing mechanical ventilation, a continuous infusion of hydrocortisone did not result in lower 90-day mortality than placebo.

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Cochrane Database Syst Rev. 2017 Dec 13;12:CD007720. doi: 10.1002/14651858.CD007720.pub3.

Corticosteroids for pneumonia.

Stern A, Skalsky K, Avni T, Carrara E, Leibovici L, Paul M.

BACKGROUND: Pneumonia is a common and potentially serious illness. Corticosteroids have been suggested for the treatment of different types of infection, however their role in the treatment of pneumonia remains unclear. This is an update of a review published in 2011.

OBJECTIVES: To assess the efficacy and safety of corticosteroids in the treatment of pneumonia.

SEARCH METHODS: We searched the Cochrane Acute Respiratory Infections Group's Specialised Register, CENTRAL, MEDLINE, Embase, and LILACS on 3 March 2017, together with relevant conference proceedings and references of identified trials. We also searched three trials registers for ongoing and unpublished trials.

SELECTION CRITERIA: We included randomised controlled trials (RCTs) that assessed systemic corticosteroid therapy, given as adjunct to antibiotic treatment, versus placebo or no corticosteroids for adults and children with pneumonia.

DATA COLLECTION AND ANALYSIS: We used standard methodological procedures expected by Cochrane. Two review authors independently assessed risk of bias and extracted data. We contacted study authors for additional information. We estimated risk ratios (RR) with 95% confidence intervals (CI) and pooled data using the Mantel-Haenszel fixed-effect model when possible.

MAIN RESULTS: We included 17 RCTs comprising a total of 2264 participants; 13 RCTs included 1954 adult participants, and four RCTs included 310 children. This update included 12 new studies, excluded one previously included study, and excluded five new trials. One trial awaits classification.All trials limited inclusion to inpatients with community-acquired pneumonia (CAP), with or without healthcare-associated pneumonia (HCAP). We assessed the risk of selection bias and attrition bias as low or unclear overall. We assessed performance bias risk as low for nine trials, unclear for one trial, and high for seven trials. We assessed reporting bias risk as low for three trials and high for the remaining 14 trials.Corticosteroids significantly reduced mortality in adults with severe pneumonia (RR 0.58, 95% CI 0.40 to 0.84; moderate-quality evidence), but not in adults with non-severe pneumonia (RR 0.95, 95% CI 0.45 to 2.00). Early clinical failure rates (defined as death from any cause, radiographic progression, or clinical instability at day 5 to 8) were significantly reduced with corticosteroids in people with severe and non-severe pneumonia (RR 0.32, 95% CI 0.15 to 0.7; and RR 0.68, 95% CI 0.56 to 0.83, respectively; high-quality evidence). Corstocosteroids reduced time to clinical cure, length of hospital and intensive care unit stays, development of respiratory failure or shock not present at pneumonia onset, and rates of pneumonia complications.Among children with bacterial pneumonia, corticosteroids reduced early clinical failure rates (defined as for adults, RR 0.41, 95% CI 0.24 to 0.70; high-quality evidence) based on two small, clinically heterogeneous trials, and reduced time to clinical cure.Hyperglycaemia was significantly more common in adults treated with corticosteroids (RR 1.72, 95% CI 1.38 to 2.14). There were no significant differences between corticosteroid-treated people and controls for other adverse events or secondary infections (RR 1.19, 95% CI 0.73 to 1.93).

AUTHORS' CONCLUSIONS: Corticosteroid therapy reduced mortality and morbidity in adults with severe CAP; the number needed to treat for an additional beneficial outcome was 18 patients (95% CI 12 to 49) to prevent one death. Corticosteroid therapy reduced morbidity, but not mortality, for adults and children with non-severe CAP. Corticosteroid therapy was associated with more adverse events, especially hyperglycaemia, but the harms did not seem to outweigh the benefits.

PMID: 29236286

Lancet Infect Dis. 2018 Apr;18(4):391-400. doi: 10.1016/S1473-3099(18)30099-9. Epub 2018 Feb 16.

Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial.

Paul M, Daikos GL, Durante-Mangoni E, Yahav D, Carmeli Y, Benattar YD, Skiada A, Andini R, Eliakim-Raz N, Nutman A, Zusman O, Antoniadou A, Pafundi PC, Adler A, Dickstein Y, Pavleas I, Zampino R, Daitch V, Bitterman R, Zayyad H, Koppel F, Levi I, Babich T, Friberg LE, Mouton JW, Theuretzbacher U, Leibovici L.

BACKGROUND: Colistin-carbapenem combinations are synergistic in vitro against carbapenem-resistant Gram-negative bacteria. We aimed to test whether combination therapy improves clinical outcomes for adults with infections caused by carbapenem-resistant or carbapenemase-producing Gram-negative bacteria.

METHODS: A randomised controlled superiority trial was done in six hospitals in Israel, Greece, and Italy. We included adults with bacteraemia, ventilator-associated pneumonia, hospital-acquired pneumonia, or urosepsis caused by carbapenem-non-susceptible Gram-negative bacteria. Patients were randomly assigned (1:1) centrally, by computer-generated permuted blocks stratified by centre, to intravenous colistin (9-million unit loading dose, followed by 4·5 million units twice per day) or colistin with meropenem (2-g prolonged infusion three times per day). The trial was open-label, with blinded outcome assessment. Treatment success was defined as survival, haemodynamic stability, improved or stable Sequential Organ Failure Assessment score, stable or improved ratio of partial pressure of arterial oxygen to fraction of expired oxygen for patients with pneumonia, and microbiological cure for patients with bacteraemia. The primary outcome was clinical failure, defined as not meeting all success criteria by intention-to-treat analysis, at 14 days after randomisation. This trial is registered at ClinicalTrials.gov, number NCT01732250, and is closed to accrual.

FINDINGS: Between Oct 1, 2013, and Dec 31, 2016, we randomly assigned 406 patients to the two treatment groups. Most patients had pneumonia or bacteraemia (355/406, 87%), and most infections were caused by Acinetobacter baumannii (312/406, 77%). No significant difference between colistin monotherapy (156/198, 79%) and combination therapy (152/208, 73%) was observed for clinical failure at 14 days after randomisation (risk difference -5·7%, 95% CI -13·9 to 2·4; risk ratio [RR] 0·93, 95% CI 0·83-1·03). Results were similar among patients with A baumannii infections (RR 0·97, 95% CI 0·87-1·09). Combination therapy increased the incidence of diarrhoea (56 [27%] vs 32 [16%] patients) and decreased the incidence of mild renal failure (37 [30%] of 124 vs 25 [20%] of 125 patients at risk of or with kidney injury).

INTERPRETATION: Combination therapy was not superior to monotherapy. The addition of meropenem to colistin did not improve clinical failure in severe A baumannii infections. The trial was unpowered to specifically address other bacteria.

PMID: 29456043

Lancet. 2018 Feb 17;391(10121):668-678. doi: 10.1016/S0140-6736(17)32456-X. Epub 2017 Dec 14.

Adjunctive rifampicin for Staphylococcus aureus bacteraemia (ARREST): a multicentre, randomised, double-blind, placebo-controlled trial.

Thwaites GE, Scarborough M, Szubert A, Nsutebu E, Tilley R, Greig J, Wyllie SA, Wilson P, Auckland C, Cairns J, Ward D, Lal P, Guleri A, Jenkins N, Sutton J, Wiselka M, Armando GR, Graham C, Chadwick PR, Barlow G, Gordon NC, Young B, Meisner S, McWhinney P, Price DA, Harvey D, Nayar D, Jeyaratnam D, Planche T, Minton J, Hudson F, Hopkins S, Williams J, Török ME, Llewelyn MJ, Edgeworth JD, Walker AS; United Kingdom Clinical Infection Research Group (UKCIRG).

BACKGROUND: Staphylococcus aureus bacteraemia is a common cause of severe community-acquired and hospital-acquired infection worldwide. We tested the hypothesis that adjunctive rifampicin would reduce bacteriologically confirmed treatment failure or disease recurrence, or death, by enhancing early S aureus killing, sterilising infected foci and blood faster, and reducing risks of dissemination and metastatic infection.

METHODS: In this multicentre, randomised, double-blind, placebo-controlled trial, adults (≥18 years) with S aureus bacteraemia who had received ≤96 h of active antibiotic therapy were recruited from 29 UK hospitals. Patients were randomly assigned (1:1) via a computer-generated sequential randomisation list to receive 2 weeks of adjunctive rifampicin (600 mg or 900 mg per day according to weight, oral or intravenous) versus identical placebo, together with standard antibiotic therapy. Randomisation was stratified by centre. Patients, investigators, and those caring for the patients were masked to group allocation. The primary outcome was time to bacteriologically confirmed treatment failure or disease recurrence, or death (all-cause), from randomisation to 12 weeks, adjudicated by an independent review committee masked to the treatment. Analysis was intention to treat. This trial was registered, number ISRCTN37666216, and is closed to new participants.

FINDINGS: Between Dec 10, 2012, and Oct 25, 2016, 758 eligible participants were randomly assigned: 370 to rifampicin and 388 to placebo. 485 (64%) participants had community-acquired S aureus infections, and 132 (17%) had nosocomial S aureus infections. 47 (6%) had meticillin-resistant infections. 301 (40%) participants had an initial deep infection focus. Standard antibiotics were given for 29 (IQR 18-45) days; 619 (82%) participants received flucloxacillin. By week 12, 62 (17%) of participants who received rifampicin versus 71 (18%) who received placebo experienced treatment failure or disease recurrence, or died (absolute risk difference -1·4%, 95% CI -7·0 to 4·3; hazard ratio 0·96, 0·68-1·35, p=0·81). From randomisation to 12 weeks, no evidence of differences in serious (p=0·17) or grade 3-4 (p=0·36) adverse events were observed; however, 63 (17%) participants in the rifampicin group versus 39 (10%) in the placebo group had antibiotic or trial drug-modifying adverse events (p=0·004), and 24 (6%) versus six (2%) had drug interactions (p=0·0005).

INTERPRETATION: Adjunctive rifampicin provided no overall benefit over standard antibiotic therapy in adults with S aureus bacteraemia.

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PMCID: PMC5820409

Lancet Infect Dis. 2017 Jul;17(7):735-744. doi: 10.1016/S1473-3099(17)30235-9. Epub 2017 Apr 28.

Efficacy and safety of ridinilazole compared with vancomycin for the treatment of Clostridium difficile infection: a phase 2, randomised, double-blind, active-controlled, non-inferiority study.

Vickers RJ, Tillotson GS, Nathan R, Hazan S, Pullman J, Lucasti C, Deck K, Yacyshyn B, Maliakkal B, Pesant Y, Tejura B, Roblin D, Gerding DN, Wilcox MH; CoDIFy study group.

BACKGROUND: Clostridium difficile infection is the most common health-care-associated infection in the USA. We assessed the safety and efficacy of ridinilazole versus vancomycin for treatment of C difficile infection.

METHODS: We did a phase 2, randomised, double-blind, active-controlled, non-inferiority study. Participants with signs and symptoms of C difficile infection and a positive diagnostic test result

were recruited from 33 centres in the USA and Canada and randomly assigned (1:1) to receive oral ridinilazole (200 mg every 12 h) or oral vancomycin (125 mg every 6 h) for 10 days. The primary endpoint was achievement of a sustained clinical response, defined as clinical cure at the end of treatment and no recurrence within 30 days, which was used to establish non-inferiority (15% margin) of ridinilazole versus vancomycin. The primary efficacy analysis was done on a modified intention-to-treat population comprising all individuals with C difficile infection confirmed by the presence of free toxin in stool who were randomly assigned to receive one or more doses of the study drug. The study is registered with ClinicalTrials.gov, number NCT02092935.

FINDINGS: Between June 26, 2014, and August 31, 2015, 100 patients were recruited; 50 were randomly assigned to receive ridinilazole and 50 to vancomycin. 16 patients did not complete the study, and 11 discontinued treatment early. The primary efficacy analysis included 69 patients (n=36 in the ridinilazole group; n=33 in the vancomycin group). 24 of 36 (66·7%) patients in the ridinilazole group versus 14 of 33 (42·4%) of those in the vancomycin group had a sustained clinical response (treatment difference 21·1%, 90% CI 3·1-39·1, p=0·0004), establishing the non-inferiority of ridinilazole and also showing statistical superiority at the 10% level. Ridinilazole was well tolerated, with an adverse event profile similar to that of vancomycin: 82% (41 of 50) of participants reported adverse events in the ridinilazole group and 80% (40 of 50) in the vancomycin group. There were no adverse events related to ridinilazole that led to discontinuation.

INTERPRETATION: Ridinilazole is a targeted-spectrum antimicrobial that shows potential in treatment of initial C difficile infection and in providing sustained benefit through reduction in disease recurrence. Further clinical development is warranted.

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PMCID: PMC5483507

Cochrane Database Syst Rev. 2017 Dec 19;12:CD006095. doi: 10.1002/14651858.CD006095.pub4.

Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children.

Goldenberg JZ, Yap C, Lytvyn L, Lo CK, Beardsley J, Mertz D, Johnston BC.

BACKGROUND: Antibiotics can disturb gastrointestinal microbiota which may lead to reduced resistance to pathogens such as Clostridium difficile (C. difficile). Probiotics are live microbial preparations that, when administered in adequate amounts, may confer a health benefit to the host, and are a potential C. difficile prevention strategy. Recent clinical practice guidelines do not recommend probiotic prophylaxis, even though probiotics have the highest quality evidence among cited prophylactic therapies.

OBJECTIVES: To assess the efficacy and safety of probiotics for preventing C.difficile-associated diarrhea (CDAD) in adults and children.

SEARCH METHODS: We searched PubMed, EMBASE, CENTRAL, and the Cochrane IBD Group Specialized Register from inception to 21 March 2017. Additionally, we conducted an extensive grey literature search.

SELECTION CRITERIA: Randomized controlled (placebo, alternative prophylaxis, or no treatment control) trials investigating probiotics (any strain, any dose) for prevention of CDAD, or C. difficile infection were considered for inclusion.

DATA COLLECTION AND ANALYSIS: Two authors (independently and in duplicate) extracted data and assessed risk of bias. The primary outcome was the incidence of CDAD. Secondary outcomes

included detection of C. difficile infection in stool, adverse events, antibiotic-associated diarrhea (AAD) and length of hospital stay. Dichotomous outcomes (e.g. incidence of CDAD) were pooled using a random-effects model to calculate the risk ratio (RR) and corresponding 95% confidence interval (95% CI). We calculated the number needed to treat for an additional beneficial outcome (NNTB) where appropriate. Continuous outcomes (e.g. length of hospital stay) were pooled using a random-effects model to calculate the mean difference and corresponding 95% CI. Sensitivity analyses were conducted to explore the impact of missing data on efficacy and safety outcomes. For the sensitivity analyses, we assumed that the event rate for those participants in the control group who had missing data was the same as the event rate for those participants in the control group who were successfully followed. For the probiotic group, we calculated effects using the following assumed ratios of event rates in those with missing data in comparison to those successfully followed: 1.5:1, 2:1, 3:1, and 5:1. To explore possible explanations for heterogeneity, a priori subgroup analyses were conducted on probiotic species, dose, adult versus pediatric population, and risk of bias as well as a post hoc subgroup analysis on baseline risk of CDAD (low 0% to 2%; moderate 3% to 5%; high > 5%). The overall quality of the evidence supporting each outcome was independently assessed using the GRADE criteria**.**

MAIN RESULTS: Thirty-nine studies (9955 participants) met the eligibility requirements for our review. Overall, 27 studies were rated as either high or unclear risk of bias. A complete case analysis (i.e. participants who completed the study) among trials investigating CDAD (31 trials, 8672 participants) suggests that probiotics reduce the risk of CDAD by 60%. The incidence of CDAD was 1.5% (70/4525) in the probiotic group compared to 4.0% (164/4147) in the placebo or no treatment control group (RR 0.40, 95% CI 0.30 to 0.52; GRADE = moderate). Twenty-two of 31 trials had missing CDAD data ranging from 2% to 45%. Our complete case CDAD results proved robust to sensitivity analyses of plausible and worst-plausible assumptions regarding missing outcome data and results were similar whether considering subgroups of trials in adults versus children, inpatients versus outpatients, different probiotic species, lower versus higher doses of probiotics, or studies at high versus low risk of bias. However, in a post hoc analysis, we did observe a subgroup effect with respect to baseline risk of developing CDAD. Trials with a baseline CDAD risk of 0% to 2% and 3% to 5% did not show any difference in risk but trials enrolling participants with a baseline risk of > 5% for developing CDAD demonstrated a large 70% risk reduction (interaction P value = 0.01). Among studies with a baseline risk > 5%, the incidence of CDAD in the probiotic group was 3.1% (43/1370) compared to 11.6% (126/1084) in the control group (13 trials, 2454 participants; RR 0.30, 95% CI 0.21 to 0.42; GRADE = moderate). With respect to detection of C. difficile in the stool pooled complete case results from 15 trials (1214 participants) did not show a reduction in infection rates. C. difficile infection was 15.5% (98/633) in the probiotics group compared to 17.0% (99/581) in the placebo or no treatment control group (RR 0.86, 95% CI 0.67 to 1.10; GRADE = moderate). Adverse events were assessed in 32 studies (8305 participants) and our pooled complete case analysis indicates probiotics reduce the risk of adverse events by 17% (RR 0.83, 95% CI 0.71 to 0.97; GRADE = very low). In both treatment and control groups the most common adverse events included abdominal cramping, nausea, fever, soft stools, flatulence, and taste disturbance.

AUTHORS' CONCLUSIONS: Based on this systematic review and meta-analysis of 31 randomized controlled trials including 8672 patients, moderate certainty evidence suggests that probiotics are effective for preventing CDAD (NNTB = 42 patients, 95% CI 32 to 58). Our post hoc subgroup analyses to explore heterogeneity indicated that probiotics are effective among trials with a CDAD baseline risk >5% (NNTB = 12; moderate certainty evidence), but not among trials with a baseline risk ≤5% (low to moderate certainty evidence). Although adverse effects were reported among 32 included trials, there were more adverse events among patients in the control groups. The short-term use of probiotics appears to be safe and effective when used along with antibiotics in patients who are not immunocompromised or severely debilitated. Despite the need for further research,

hospitalized patients, particularly those at high risk of CDAD, should be informed of the potential benefits and harms of probiotics

PMID: 29257353.

Clin Infect Dis. 2018 Jan 6;66(2):198-205. doi: 10.1093/cid/cix819.

Metformin Use Reverses the Increased Mortality Associated With Diabetes Mellitus During Tuberculosis Treatment.

Degner NR, Wang JY, Golub JE, Karakousis PC.

BACKGROUND: The global type 2 diabetes mellitus (DM) epidemic threatens progress made in reducing tuberculosis (TB)-related mortality worldwide. Previous clinical studies have not fully evaluated potential confounding variables in addressing the impact of DM on TB treatment outcomes. The antidiabetic agent metformin regulates autophagy and may play a role as a host-directed therapeutic adjuvant to antitubercular treatment.

METHODS: We conducted a retrospective cohort study comprising patients aged ≥13 years undergoing treatment for culture-confirmed, drug-susceptible pulmonary TB. We assessed the effect of DM on mortality during TB treatment and 2-month TB sputum-culture conversion. We also evaluated the effect of metformin use on survival during TB treatment.

RESULTS: Among 2416 patients undergoing TB treatment, after adjusting for age, sex, chronic kidney disease, cancer, hepatitis C, tobacco use, cavitary disease, and treatment adherence, patients with DM had 1.91 times higher odds (95% confidence interval [CI], 1.51-2.40) of death during TB treatment than patients without DM, and 1.72 (95% CI, 1.25-2.38) times higher odds of remaining culture-positive at 2 months. Metformin use in patients with DM was significantly associated with decreased mortality during TB treatment (hazard ratio, 0.56 [95% CI, .39-.82]), and metformin users had similar mortality as patients without DM.

CONCLUSIONS: This study suggests that despite multiple potential confounding variables, DM poses an increased risk of adverse TB treatment outcomes. There was a significant association between metformin use and decreased mortality during TB treatment, suggesting a potential role for this agent as adjunctive, host-directed therapy.

PMID: 29325084
PMCID: PMC5848303

Clin Infect Dis. 2018 Jan 18;66(3):329-336. doi: 10.1093/cid/cix794.

The Impact of a Reported Penicillin Allergy on Surgical Site Infection Risk.

Blumenthal KG, Ryan EE, Li Y, Lee H, Kuhlen JL, Shenoy ES.

BACKGROUND: A reported penicillin allergy may compromise receipt of recommended antibiotic prophylaxis intended to prevent surgical site infections (SSIs). Most patients with a reported penicillin allergy are not allergic. We determined the impact of a reported penicillin allergy on the development of SSIs.

METHODS: In this retrospective cohort study of Massachusetts General Hospital hip arthroplasty, knee arthroplasty, hysterectomy, colon surgery, and coronary artery bypass grafting patients from 2010 to 2014, we compared patients with and without a reported penicillin allergy. The primary outcome was an SSI, as defined by the Centers for Disease Control and Prevention's National Healthcare Safety Network. The secondary outcome was perioperative antibiotic use.

RESULTS: Of 8385 patients who underwent 9004 procedures, 922 (11%) reported a penicillin allergy, and 241 (2.7%) had an SSI. In multivariable logistic regression, patients reporting a penicillin allergy had increased odds (adjusted odds ratio, 1.51; 95% confidence interval, 1.02-2.22) of SSI. Penicillin allergy reporters were administered less cefazolin (12% vs 92%; P < .001) and more clindamycin (49% vs 3%; P < .001), vancomycin (35% vs 3%; P < .001), and gentamicin (24% vs 3%; P < .001) compared with those without a reported penicillin allergy. The increased SSI risk was entirely mediated by the patients' receipt of an alternative perioperative antibiotic; between 112 and 124 patients with reported penicillin allergy would need allergy evaluation to prevent 1 SSI.

CONCLUSIONS: Patients with a reported penicillin allergy had a 50% increased odds of SSI, attributable to the receipt of second-line perioperative antibiotics. Clarification of penicillin allergies as part of routine preoperative care may decrease SSI risk.

PMID: 29361015
PMCID: PMC5850334

Clin Infect Dis. 2017 Jun 1. doi: 10.1093/cid/cix512. [Epub ahead of print]

Point-of-care Beta-lactam Allergy Skin Testing by Antimicrobial Stewardship Programs: A Pragmatic Multicenter Prospective Evaluation.

Leis JA, Palmay L, Ho G, Raybardhan S, Gill S, Kan T, Campbell J, Kiss A, McCready JB, Das P, Minnema B, Powis JE, Walker SAN, Ferguson H, Wong B, Weber E.

BACKGROUND: Beta-lactam allergy skin testing (BLAST) is recommended by antimicrobial stewardship program (ASP) guidelines, yet few studies have systematically evaluated its impact when delivered at point-of-care.

METHODS: We conducted a pragmatic multicenter prospective evaluation of the use of point-of-care BLAST by ASPs. In staggered 3-month intervals, ASP teams at three hospitals received training by allergists to offer BLAST for eligible patients with infectious diseases receiving non-preferred beta-lactam therapy due to severity of their allergy. The primary outcome was the proportion of patients receiving the preferred beta-lactam therapy.

RESULTS: Of 827 patients with reported beta-lactam allergy over 15-months, beta-lactam therapy was preferred among 632(76%). During baseline periods, 50% (124/246) received preferred beta-lactam therapy based on history, compared with 60% (232/386) during the intervention periods (p=0.02), which improved further to 81% (313/386) upon provision of BLAST (p<0.001) without any increase in incidence of adverse drug reactions (4% vs. 3%; p=0.4). After adjusting for patient variables and the correlation between hospitals, the intervention period was associated with a 4.5-fold greater odds of receiving preferred beta-lactam therapy (95% CI, 2.4-8.2; p<0.0001).

CONCLUSIONS: The use of BLAST at the point-of-care across three hospital ASPs resulted in greater use of preferred beta-lactam therapy without increasing the risk of adverse drug reactions. Longer term studies are needed to better assess the safety and clinical impact of this ASP intervention.

PMID: 28575226

JAMA. 2016 Jul 12;316(2):191-210. doi: 10.1001/jama.2016.8900.

Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2016 Recommendations of the International Antiviral Society-USA Panel.

Günthard HF, Saag MS, Benson CA, del Rio C, Eron JJ, Gallant JE, Hoy JF, Mugavero MJ, Sax PE, Thompson MA, Gandhi RT, Landovitz RJ, Smith DM, Jacobsen DM, Volberding PA.

IMPORTANCE: New data and therapeutic options warrant updated recommendations for the use of antiretroviral drugs (ARVs) to treat or to prevent HIV infection in adults.

OBJECTIVE: To provide updated recommendations for the use of antiretroviral therapy in adults (aged ≥18 years) with established HIV infection, including when to start treatment, initial regimens, and changing regimens, along with recommendations for using ARVs for preventing HIV among those at risk, including preexposure and postexposure prophylaxis.

EVIDENCE REVIEW:A panel of experts in HIV research and patient care convened by the International Antiviral Society-USA reviewed data published in peer-reviewed journals, presented by regulatory agencies, or presented as conference abstracts at peer-reviewed scientific conferences since the 2014 report, for new data or evidence that would change previous recommendations or their ratings. Comprehensive literature searches were conducted in the PubMed and EMBASE databases through April 2016. Recommendations were by consensus, and each recommendation was rated by strength and quality of the evidence.

FINDINGS: Newer data support the widely accepted recommendation that antiretroviral therapy should be started in all individuals with HIV infection with detectable viremia regardless of CD4 cell count. Recommended optimal initial regimens for most patients are 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus an integrase strand transfer inhibitor (InSTI). Other effective regimens include nonnucleoside reverse transcriptase inhibitors or boosted protease inhibitors with 2 NRTIs. Recommendations for special populations and in the settings of opportunistic infections and concomitant conditions are provided. Reasons for switching therapy include convenience, tolerability, simplification, anticipation of potential new drug interactions, pregnancy or plans for pregnancy, elimination of food restrictions, virologic failure, or drug toxicities. Laboratory assessments are recommended before treatment, and monitoring during treatment is recommended to assess response, adverse effects, and adherence. Approaches are recommended to improve linkage to and retention in care are provided. Daily tenofovir disoproxil fumarate/emtricitabine is

recommended for use as preexposure prophylaxis to prevent HIV infection in persons at high risk. When indicated, postexposure prophylaxis should be started as soon as possible after exposure.

CONCLUSIONS AND RELEVANCE: Antiretroviral agents remain the cornerstone of HIV treatment and prevention. All HIV-infected individuals with detectable plasma virus should receive treatment with recommended initial regimens consisting of an InSTI plus 2 NRTIs. Preexposure prophylaxis should be considered as part of an HIV prevention strategy for at-risk individuals. When used effectively, currently available ARVs can sustain HIV suppression and can prevent new HIV infection. With these treatment regimens, survival rates among HIV-infected adults who are retained in care can approach those of uninfected adults.

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Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial.

Gallant J, Lazzarin A, Mills A, Orkin C, Podzamczer D, Tebas P, Girard PM, Brar I, Daar ES, Wohl D, Rockstroh J, Wei X, Custodio J, White K, Martin H, Cheng A, Quirk E.

BACKGROUND: Integrase strand transfer inhibitors (INSTIs) are recommended components of initial antiretroviral therapy with two nucleoside reverse transcriptase inhibitors. Bictegravir is a novel, potent INSTI with a high in-vitro barrier to resistance and low potential as a perpetrator or victim of clinically relevant drug-drug interactions. We aimed to assess the efficacy and safety of bictegravir coformulated with emtricitabine and tenofovir alafenamide as a fixed-dose combination versus coformulated dolutegravir, abacavir, and lamivudine.

METHODS: We did this double-blind, multicentre, active-controlled, randomised controlled non-inferiority trial at 122 outpatient centres in nine countries in Europe, Latin America, and North America. We enrolled HIV-1 infected adults (aged ≥18 years) who were previously untreated (HIV-1 RNA ≥500 copies per mL); HLA-B*5701-negative; had no hepatitis B virus infection; screening genotypes showing sensitivity to emtricitabine, tenofovir, lamivudine, and abacavir; and an estimated glomerular filtration rate of 50 mL/min or more. Participants were randomly assigned (1:1), via a computer-generated allocation sequence (block size of four), to receive coformulated bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg or coformulated dolutegravir 50 mg, abacavir 600 mg, and lamivudine 300 mg, with matching placebo, once daily for 144 weeks. Randomisation was stratified by HIV-1 RNA (≤100 000 copies per mL, >100 000 to ≤400 000 copies per mL, or >400 000 copies per mL), CD4 count (<50 cells per µL, 50-199 cells per µL, or ≥200 cells per µL), and region (USA or ex-USA). Investigators, participants, and study staff giving treatment, assessing outcomes, and collecting data were masked to group assignment. The primary endpoint was the proportion of participants with plasma HIV-1 RNA less than 50 copies per mL at week 48, as defined by the US Food and Drug Administration snapshot algorithm, with a prespecified non-inferiority margin of -12%. All participants who received one dose of study drug were included in primary efficacy and safety analyses. This trial is registered with ClinicalTrials.gov, number NCT02607930.

FINDINGS: Between Nov 13, 2015, and July 14, 2016, we randomly assigned 631 participants to receive coformulated bictegravir, emtricitabine, and tenofovir alafenamide (n=316) or coformulated dolutegravir, abacavir, and lamivudine (n=315), of whom 314 and 315 patients, respectively, received

at least one dose of study drug. At week 48, HIV-1 RNA less than 50 copies per mL was achieved in 92·4% of patients (n=290 of 314) in the bictegravir, emtricitabine, and tenofovir alafenamide group and 93·0% of patients (n=293 of 315) in the dolutegravir, abacavir, and lamivudine group (difference -0·6%, 95·002% CI -4·8 to 3·6; p=0·78), demonstrating non-inferiority of bictegravir, emtricitabine, and tenofovir alafenamide to dolutegravir, abacavir, and lamivudine. No individual developed treatment-emergent resistance to any study drug. Incidence and severity of adverse events was mostly similar between groups except for nausea, which occurred less frequently in patients given bictegravir, emtricitabine, and tenofovir alafenamide than in those given dolutegravir, abacavir, and lamivudine (10% [n=32] vs 23% [n=72]; p<0·0001). Adverse events related to study drug were less common with bictegravir, emtricitabine, and tenofovir alafenamide than with dolutegravir, abacavir, and lamivudine (26% [n=82] vs 40% [n=127]), the difference being driven by a higher incidence of drug-related nausea in the dolutegravir, abacavir, and lamivudine group (5% [n=17] vs 17% [n=55]; p<0·0001).

INTERPRETATION: At 48 weeks, coformulated bictegravir, emtricitabine, and tenofovir alafenamide achieved virological suppression in 92% of previously untreated adults and was non-inferior to coformulated dolutegravir, abacavir, and lamivudine, with no treatment-emergent resistance. Bictegravir, emtricitabine, and tenofovir alafenamide was safe and well tolerated with better gastrointestinal tolerability than dolutegravir, abacavir, and lamivudine. Because coformulated bictegravir, emtricitabine, and tenofovir alafenamide does not require HLA B*5701 testing and provides guideline-recommended treatment for individuals co-infected with HIV and hepatitis B, this regimen might lend itself to rapid or same-day initiation of therapy in the clinical setting.

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Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial.

Molina JM, Squires K, Sax PE, Cahn P, Lombaard J, DeJesus E, Lai MT, Xu X, Rodgers A, Lupinacci L, Kumar S, Sklar P, Nguyen BY, Hanna GJ, Hwang C; DRIVE-FORWARD Study Group

BACKGROUND: Doravirine is a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) with a pharmacokinetic profile supporting once-daily dosing, and potent in-vitro activity against the most common NNRTI-resistant HIV-1 variants. We compared doravirine with ritonavir-boosted darunavir, when both were given with two nucleoside reverse transcriptase inhibitors (NRTIs), in adults with previously untreated HIV-1 infection.

METHODS: In this randomised, controlled, double-blind, multicentre, non-inferiority trial, adults with HIV-1 infection were screened and enrolled at 125 clinical centres in 15 countries. Eligible participants (aged ≥18 years) were naive to antiretroviral therapy with plasma HIV-1 RNA of at least 1000 copies per mL at screening. Participants who had previously been treated for a viral infection other than HIV-1, those taking immunosuppressive drugs, and individuals with active acute hepatitis were excluded. Participants were randomly assigned (1:1) via an interactive voice and web response system to receive oral doravirine 100 mg or darunavir 800 mg plus ritonavir 100 mg once daily, with two investigator-selected NRTIs (tenofovir and emtricitabine or abacavir and lamivudine) for up to 96 weeks. Randomisation was stratified by HIV-1 RNA measurements at screening (≤100 000 vs >100 000 copies per mL) and the NRTI pair. Study participants, funding institution staff, investigators,

and study site personnel were masked to treatment group assignment. The primary efficacy endpoint was the proportion of participants achieving HIV-1 RNA of less than 50 copies per mL at week 48 defined by the US Food and Drug Administration snapshot algorithm, with non-inferiority established if the lower bound of the two-sided 95% CI for the treatment difference (doravirine minus darunavir) was greater than -10 percentage points. All participants who received at least one dose of study drug were included in the primary efficacy and safety analyses. This trial is active, but not recruiting, and is registered with ClinicalTrials.gov, number NCT02275780.

FINDINGS: Between Dec 1, 2014, and Oct 20, 2015, 1027 participants were screened for eligibility, of whom 769 participants were randomly assigned to treatment (385 with doravirine and 384 with ritonavir-boosted darunavir). 56 participants discontinued treatment in the doravirine group compared with 71 in the darunavir group, mostly due to loss to follow-up. 383 participants who received doravirine and 383 who received darunavir were included in the primary efficacy analyses. At week 48, 321 (84%) participants in the doravirine group and 306 (80%) in the darunavir group achieved plasma HIV-1 RNA of less than 50 copies per mL (difference 3·9%, 95% CI -1·6 to 9·4), indicating non-inferiority of the doravirine regimen. The most common study drug-related adverse events were diarrhoea (21 [5%] of 383 participants in the doravirine group and 49 [13%] of 383 participants in the darunavir group), nausea (25 [7%] vs 29 [8%]), and headache (23 [6%] vs ten [3%]). 18 participants (six [2%] of 383 participants in the doravirine group vs 12 [3%] of 383 participants in the darunavir group) discontinued treatment due to adverse events, which were considered drug-related in four (1%) participants in the doravirine group and 8 (2%) participants in the darunavir group. Serious adverse events occurred in 19 (5%) of 383 participants in the doravirine group and 23 (6%) of 383 in the darunavir roup, and were considered study-drug related in one (<1%) participant of each group.

INTERPRETATION: In treatment-naive adults with HIV-1 infection, doravirine combined with two NRTIs might offer a valuable treatment option for adults with previously untreated HIV-1 infection.

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European AIDS Clinical Society Conference, Milano, 2017. Abstract PS1/1.

Individual Patient Data Meta-analysis of Randomized Controlled Trials of Dual Therapy with a Boosted Protease Inhibitor Plus Lamivudine for Maintenance of Virological Suppression (Gesida Study 9717).

Perez-Molina, F. Pulido, S. Di Giambenedetto, E. Ribera, S. Moreno, J. Zamora, C. Coscia, J.M. Gatell, A. De Luca, J.R. Arribas

OBJECTIVES: To compare the efficacy of switching to a boosted protease inhibitor (PI) plus lamivudine Dual Therapy (DT) vs. continuation of triple therapy (TT) with two nucleos(t)ides plus a PI for maintenance of virological suppression and whether efficacy was modified by gender, active HCV infection and type of PI.

METHODS: We performed a systematic search of PubMed, EmBase, BIOSIS, Cochrane-CRCT and of the main scientific meetings about HIV infection (Jan/1990-Mar/2017). Only randomized controlled trials were included. Principal investigators were contacted and agreed to share study databases. Primary endpoint was to demonstrate the non-inferiority of DT vs. TT with the current FDA endpoint (4% non-inferiority margin for virologic failure defined as HIV-RNA≥50 cop/mL at week 48; snapshot algorithm). We also analysed the difference in the proportion of patients with HIV-RNA< 50 cop/mL

at week 48 (non-inferiority margin: 12%). Effect estimates and 95%CI were calculated using GEE models.

RESULTS: We found 886 references that finally yielded 9 articles corresponding to 4 clinical trials: ATLAS-M, SALT, DUAL and OLE (1051 patients). The studies were reanalysed under the same conditions than the original analysis to check for consistency. At week 48, 4% of patients on DT vs. 3.04% on TT had HIV-RNA≥50 cop/mL: difference 0.9% (95%CI, -1.2% to 3.1%) (Figure). Also, at week 48, 84.7% of patients on DT vs. 83.2% on TT had HIV-RNA< 50 cop/mL: difference 1.4% (95%CI, -2.8% to 5.8%). Gender, active HCV infection or type of PI had no effect on treatment efficacy differences between DT and TT (non-significant interactions).

CONCLUSION: In this invidual patient data meta-analysis of 1051 participants, DT was non-inferior to TT using both current and past FDA end-points for trials of antiretroviral therapy switch. The efficacy of DT was not influenced by patient's gender, active HCV infection status or type of PI.

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Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies.

Llibre JM, Hung CC, Brinson C, Castelli F, Girard PM, Kahl LP, Blair EA, Angelis K, Wynne B, Vandermeulen K, Underwood M, Smith K, Gartland M, Aboud M.

BACKGROUND: Lifelong HIV antiretroviral therapy (ART) has prompted an interest in two-drug regimens to minimise cumulative drug exposure and toxicities. The safety, tolerability, and efficacy of dolutegravir and rilpivirine suggest potential compatibility and effectiveness as a two-drug regimen. We aimed to investigate this two-drug regimen in a phase 3 study.

METHODS: We identically designed SWORD-1 and SWORD-2, which were open-label, parallel-group, multicentre, phase 3, randomised, non-inferiority studies in 12 countries evaluating efficacy and safety of once-daily dolutegravir 50 mg plus rilpivirine 25 mg versus current ART regimen (CAR). We included participants aged 18 years or older who were on first or second ART with stable plasma HIV-1 RNA (viral load <50 copies per mL) for 6 months or longer at screening. We randomly assigned participants (1:1) with stratification by third-agent class, age, and planned participation in a bone mineral density substudy. The primary endpoint was proportion of participants with viral load lower than 50 copies per mL at week 48 among those individuals who received one or more doses of study medication. Investigators monitored adverse events to assess safety. These trials are registered with ClinicalTrials.gov, numbers NCT02429791 (SWORD-1) and NCT02422797 (SWORD-2).

FINDINGS: We screened for participants from April 14, 2015, to Oct 15, 2015, for SWORD-1 and from April 21, 2015, to Sept 25, 2015, for SWORD-2. We randomly assigned 516 participants to dolutegravir-rilpivirine and 512 to continue with CAR. At week 48 (last patient visit was Nov 22, 2016), in the pooled analysis of the intention-to-treat population, 95% of participants had viral loads lower than 50 copies per mL in each group (486 of 513 in the dolutegravir-rilpivirine group vs 485 of 511 in the CAR group), with an adjusted treatment difference of -0·2% (95% CI -3·0 to 2·5) and showed non-inferiority with a predefined margin of -8%. 395 (77%) of 513 participants in the dolutegravir-rilpivirine group and 364 (71%) of 511 participants in the CAR group reported adverse events. The most common adverse events were nasopharyngitis (49 [10%] for dolutegravir-rilpivirine vs 50 [10%] for CAR) and headache (41 [8%] vs 23 [5%]). More participants taking dolutegravir-

rilpivirine (17 [3%]) reported adverse events leading to withdrawal than did participants taking CAR (three [<1%]).

INTERPRETATION: Dolutegravir-rilpivirine was non-inferior to CAR over 48 weeks in participants with HIV suppression and showed a safety profile consistent with its components. Results support the use of this two-drug regimen to maintain HIV suppression.

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CROI, February 13–16, 2017; Seattle, Washington. Abstract LB80.

The NIX-TB trial of Pretomanid, Bedaquiline and Linezolid to treat XDR-TB

Francesca Conradie, Andreas H. Diacon, Daniel Everitt, Carl Mendel, Christo van Niekerk, Pauline Howell, Kyla Comins, Mel Spigelman

Patients with Extensively Drug Resistant (XDR) tuberculosis (TB) have had limited options for treatment and high mortality. Nix-TB is an ongoing open label study in South Africa of bedaquiline (400 mg qd for 2 weeks followed by 200 mg tiw), pretomanid (200 mg qd) and linezolid (1200 mg qd) given orally for 6 months.
Participants are required to have documented XDR-TB, or MDR TB treatment intolerance or failure (TI or Fr). The primary endpoint is bacteriologic failure, relapse or clinical failure at 6 months after treatment. Participants who are culture positive at 4 mos treatment may extend treatment for 3 mos. Clinical, laboratory and sputum liquid culture evaluations are performed at baseline and wks 1, 2, 4, 6, 8 and then every 4-6 wks through treatment. Eye examinations with slit lamp are made 3 times. Participants who complete treatment are followed for 24 mos after treatment end with repeat clinical assessments and sputum cultures.
Since April 2015, 61 participants have been enrolled as of 15 December 2016 at 2 sites. 49% of the participants are HIV positive, 79% have XDR-TB and 21% have MDR TI or Fr to prior therapy. 34 have completed the 6 months of therapy with the drug regimen and 20 have been followed to the primary endpoint at 6 months after treatment. All surviving patients were culture negative by 4 mos, with 74% negative at 8 wks. 4 participants died within the first 8 wks of therapy; 3 had multi-organ TB on autopsy and 1 had a GI bleed due to erosive esophagitis. 27% had serious adverse events (AE). No surviving participants have withdrawn from the study due to any clinical AE or lab abnormalities. The expected linezolid toxicities of peripheral neuropathy (PN) and myelosuppression (MSPN) were common but manageable. 71%, of participants had at least one linezolid dose interruption (22% of all participants due to MSPN and 28% due to PN), during the 6 mos of treatment. One had peak ALT and AST > 3 X ULN and total bili > 2X ULN, but these improved and treatment restarted without a recurrence. There were 7 cases of grade 3 or 4 transaminitis and all resolved and allowed the study regimen to be continued. There were no cases of optic neuritis. As of 15 December, 2016, there has been 1 microbiological relapse.
Current results of this greatly simplified and shortened all-oral regimen for drug resistant TB are encouraging in terms of both efficacy and safety.

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Declining HCV incidence in Dutch HIV positive men who have sex with men after unrestricted access to HCV therapy.

Boerekamps A, Van den Berk GE, Fanny LN, Leyten EM, Van Kasteren ME, van Eeden A, Posthouwer D, Claassen MA, Dofferhoff AS, Verhagen DWM, Bierman WF, Lettinga KD, Kroon FP, Delsing CE, Groeneveld PH, Soetekouw R, Peters EJ, Hullegie SJ, Popping S, Van de Vijver DAMC, Boucher CA, Arends JE, Rijnders BJ.

BACKGROUND: Direct acting antivirals (DAA) cure 95% of patients infected with hepatitis C (HCV). Modeling studies predict that universal HCV treatment will lead to a decrease in the incidence of new infections but real-life data are lacking. The incidence of HCV among Dutch HIV-positive men who have sex with men (MSM) has been high for >10 years. In 2015 DAA became available to all Dutch HCV patients and resulted in a rapid treatment uptake in HIV-positive MSM. We assessed whether this uptake was followed by a decrease in the incidence of HCV infections.

METHODS: Two prospective acute HCV treatment studies enrolled patients in 17 Dutch HIV centers, having 76% of the total HIV-positive MSM population in care in the Netherlands. Patients were recruited in 2014 and 2016, the year preceding and following unrestricted DAA availability. We compared the HCV incidence in both years.

RESULTS: The acute HCV incidence decreased from 93 infections during 8290 person years of follow up in 2014 (11.2/1000 PYFU, 95% CI 9.1-13.7) to 49 during 8961 PYFU in 2016 (5.5/1000, 95% CI 4.1-7.2). The incidence rate ratio of 2016 compared with 2014 was 0.49 (95% C.I. 0.35-0.69). Simultaneously, a significant increase in the percentage positive syphilis (+2.2%) and gonorrhea (+2.8%) tests in HIV-positive MSM was observed at sexual health clinics across the Netherlands and contradicts a decrease in risk behavior as an alternative explanation.

CONCLUSIONS: Unrestricted DAA availability in the Netherlands was followed by a 51% decrease in acute HCV infections among HIV-positive MSM.

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https://ecdc.europa.eu/en/publications-data/hivaids-surveillance-europe-2017-2016-data

HIV/AIDS surveillance in Europe 2017 - 2016 data

European Center for Disease Control

Although HIV is preventable through effective public health measures, significant HIV transmission continues in Europe. In 2016, 29 444 people were diagnosed with HIV in the 31 countries of the EU/EEA, with a rate of 5.9 per 100 000. The rate was higher among men than women (8.9 versus 2.6 cases per 100 000 population).
Similar to recent years, the highest proportion of HIV diagnoses (40%) was reported to be in men who have sex with men (MSM). However, for the first time in a number of years, several countries reported a decline in new HIV diagnoses, even after adjusting for reporting delay.
While the data in this year's report indicate alarming rates and increases in new diagnoses in some parts of eastern and central Europe over the last decade, at the same time there has been a tendency towards stabilising or even decreasing rates in some EU/EEA countries.
Trends by transmission mode, for example, show that the number of HIV diagnoses among MSM in the EU/EEA decreased slightly in 2016 and the number of heterosexually acquired cases has decreased steadily over the last decade. Moreover, in the EU/EEA, the number of AIDS cases, and the number of AIDS-related deaths, has consistently declined since the mid-1990s.