Treatments for preventing recurrence of infection with Pseudomonas aeruginosa in people with cystic fibrosis

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[Intervention Protocol]

Treatments for preventing recurrence of infection with *Pseudomonas aeruginosa* in people with cystic fibrosis

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To establish whether secondary prevention strategies, using antibiotics or other therapies, increase the chances of PWCF remaining free from PA infection following successful eradication therapy.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is the commonest autosomal recessive, life-limiting condition in Caucasian populations, affecting between 70,000 (CF Foundation 2015a) and 100,000 people (CF Trust 2015a) worldwide. It is caused by defects in the gene coding for an epithelial ion channel, the cystic fibrosis transmembrane regulator (CFTR). Clinically, the disease affects multiple systems with most of the morbidity and mortality stemming from the respiratory effects. A cycle of recurrent infection, inflammation and progressive lung damage ultimately results in respiratory failure which is the primary cause of death (CF Foundation 2015b). The current median age of survival in people with CF in the UK is 28 years (CF Trust 2015b) and in the USA 29.1 years (CF Foundation 2015b), although the life expectancy of children born in 2000 is predicted to be over 50 years (Dodge 2007).

Respiratory infections in CF occur from infancy. By the age of three years 50% of children will have had an initial infection with *Pseudomonas aeruginosa* (PA) (Jones 2015). In the UK, half of people with CF (PWCF) have chronic infection with PA by their mid-twenties (CF Trust 2015b), whereas in the USA approximately half of adults with CF (over 18 years of age) have had at least one sputum culture positive for PA (CF Foundation 2015b).

If PA is neither spontaneously cleared nor eradicated with antibiotic therapy, the CF lung environment facilitates PA adaptation to a mucoid phenotype (bacteria embedded in a sticky gel) (Döring 2010; Pitt 1986). These organisms become embedded in an exopolysaccharide biofilm which protects the organism from phagocytosis (ingestion of the bacteria by an immune cell) and reduces the efficacy of antimicrobial agents (Speert 1990). Once this change has occurred, the mucoid PA is virtually impossible to eradicate (Burns 2001; Döring 2010; Hogardt 2010; Høiby 2005; Pitt 1986). If the PA infection cannot be cleared, the affected person is faced with an increased treatment burden, accelerated decline in lung function (Emerson 2002; Konstan 2007; Kosorok 2001), increased symptom severity (Nixon 2001; Zemanick 2015) and increased mortality (Emerson 2002).

Acquisition of Pseudomonas aeruginosa

Pseudomonas aeruginosa is an environmental organism and an opportunistic human pathogen - infection typically occurs where host defences are weakened. Early isolates usually have features common to environmental organisms (Burns 2001); therefore, the usual source of infection is believed to be environmental. The organism is present in soil (Peeters 2016a) and both fresh and salt water (Khan 2007; Pirnay 2005). Strains of PA identical to those isolated from newly infected PWCF were found in the homes of nine out of 50 PWCF; the temporal relationship of these isolates is unknown (Schelstraete 2008). Other potential sources identified are air pollution (Psoter 2015) and dental equipment (Barben 2008; Jensen 1997; Mainz 2015).

Ambient temperature may also affect PA acquisition. Research from Denmark from the early 1990s suggested PA infection peaked in the winter months (Johansen 1992). However, in 2013 Psoter showed an increased incidence of infection in the summer and autumn (Psoter 2013). Other investigators found that PWCF living in areas with higher ambient temperatures have a higher prevalence of PA, and acquire it earlier, than those living in cooler climates (Collaco 2011).

Certain strains of PA are transmissible between PWCF (Cheng 1996; Jones 2001). This understanding led to the introduction of patient segregation, though the risk of transmission is low without long-term close contact (Speert 1987; Speert 2002). Nosocomial PA spread in hospitals is a source of major concern, though studies have failed to find a reservoir (Jones 2003; Panagea 2005).

Isolate of PA have been identified in air samples taken from rooms with PA-positive PWCF (Jones 2003) and these can survive in airborne droplet nuclei (less than 10 µm diameter), supporting a possible airborne route of PA transmission (Clifton 2008). Knibbs subsequently demonstrated that cough aerosols generated by PWCF positive for PA contain viable organisms, which remain detectable at a distance of four metres and after 45 minutes (Knibbs 2014).

Detection of Pseudomonas aeruginosa

Microbiological samples are collected from PWCF at routine clinic appointments and at the time of a pulmonary exacerbation. The frequency of this sampling depends on national practices. Early identification of PA infection allows for eradication therapy, since at acquisition the bacterial load is usually low and the organism sensitive to antibiotics (Burns 2001; Döring 2010).

The preferred sampling method is a sputum sample, but in many cases this is not possible. Where the individual does not produce sputum, options include cough swabs, oropharyngeal culture (OPC), induced sputum and bronchoalveolar lavage (BAL) (CF Trust 2009).

Non-sputum techniques have a number of disadvantages. The gold standard is BAL, but this is invasive and requires sedation or an anaesthetic; and selective sampling may miss organisms. Any OPC positive for PA may reflect oral flora, rather than being truly representative of the lower airways (Rosenfeld 1999), and a previous study found a high proportion of false negatives when comparing OPC with BAL specimens (Ramsey 1991). Many studies, however, continue to use OPC culture for practical reasons.

For the purposes of this review therefore, detection of PA is defined as the detection of PA in any respiratory sample; however, PA serology alone will not be accepted as evidence of new infection. First infection with PA is defined as the lifetime first identification of PA in any respiratory sample.

Eradication of Pseudomonas aeruginosa

Early antibiotic therapy is effective in reducing the chance of chronic infection. A Cochrane review showed that a number of antibiotic regimens are more effective than no treatment at eradicating PA, with an effect that can be sustained for up to two years (Langton Hewer 2014). The current review follows on from this work, focusing on additional treatments given after successful eradication to prevent or delay recurrent PA acquisition in PWCF.

Many studies of PA eradication use negative respiratory culture at the end of the active treatment period to define successful eradication. The definition of eradication is crucial to understand whether a subsequent positive PA sample is truly a new infection, rather than an incompletely cleared index episode.

Up to 90% of individuals will clear their first infection, but further episodes of intermittent infection commonly occur over the subsequent months to years until chronic infection is finally established (Høiby 2005). This recurrence may be with a new strain, or with the same strain of PA, indicating either ineffective eradication or re-infection from a common source. One observational study reported that 19 PWCF followed up after successful eradication had recurrent infection within a median (standard deviation (SD)) time of 8 (5.7) months (range 3 to 25 months) (Munck 2001). In 14 out of the 19 PWCF, the new PA strain had a distinct genotypic profile and researchers concluded that the initial eradication therapy had successfully eradicated the PA infection, with the subsequent infection considered a separate event (Munck 2001). In contrast, in a further study of 41 PWCF who were followed after a first ever PA isolation, 18 re-acquired PA after a median of 7.5 months (range 2 to 55 months), 11 of whom had identical genotypes at the second isolate (Schelstraete 2010).

One definition of freedom from PA infection is "No growth of PA in the previous 12 months after a previous PA positive culture" (Lee 2003). In compromise between this definition and the definition frequently used in trials to signify successful eradication, i.e. negative PA cultures at the end of eradication therapy, the current review will define recurrent PA infection as any respiratory culture positive for PA after a six-month period of negative cultures, where cultures are performed at least three-monthly; where data are available, it will be noted whether the infection is with a new or identical strain.

Description of the intervention

The effect of antibiotic regimens to eradicate initial PA infection may be sustained for up to two years, but the risk of a future episode of infection remains (Langton Hewer 2014). Currently, individuals who have successfully eradicated PA revert to their pre-eradication treatment regimens and no ongoing secondary prevention is attempted.

Secondary prevention is the early identification and treatment of health problems prior to the appearance of symptoms (Institute for Work and Health 2015). This contrasts with primary prevention in which mechanisms are applied to the whole population or a targeted, at-risk, population to prevent an illness or event occurring. Examples of secondary prevention in the setting of infection include ongoing treatment of Mycobacterium avium complex (MAC) until the individual has had 12 months of negative sputum samples (Griffith 2007), or the use of antiviral agents to prevent recurrent episodes of herpes simplex infection in people with HIV (Nelson 2011).

Host factors, such as sputum rheology and mucus plugging, may be equally important in the re-acquisition of PA. Interventions which affect these host factors, for example, recombinant dornase alfa (rhDNase) or hypertonic saline may also have an effect on recurrence. The administration of a further course of oral, inhaled or intravenous antibiotics, after eradication of PA is complete, may reduce the risk of recurrent infection. It is possible that CFTR modulators may affect PA isolation after eradication. Finally, immunotherapy such as IgY (derived from the eggs of hens immunised against PA) may have a role in secondary prevention.

How the intervention might work

In people with established PA infection, antibiotics are used to reduce inflammation, to maintain lung function and to reduce the chance of a pulmonary exacerbation (CF Trust 2009; Mogayzel 2014). These antibiotics are administered orally, via nebuliser or in combination with the addition of regular cycled intravenous antibiotics as the disease course progresses (CF Trust 2009).

In a retrospective study looking at nebulised gentamicin as primary prevention for the acquisition of PA, children meeting high-risk criteria for the development of PA infection were treated for a period of three years (Heinzel 2002). In the event of a further high-risk incident, treatment was continued until three years after the last high-risk event. A final audit of these children in 1999 showed that all those who continued on inhaled gentamicin remained free of PA, while seven out of 16 children who stopped prophylaxis (preventative treatment) developed chronic infection (P = 0.01).

Secondary prevention in the form of a similar prolonged course of treatment could sustain the benefits achieved by eradication, delaying the development of chronic PA infection and the subsequent negative consequences.

Why it is important to do this review

Long-term antibiotic therapy may be beneficial in delaying chronic PA infection, but it exposes individuals to the risk of adverse events (side effects of treatment, for example, allergy, damage to hearing or kidney function). Furthermore, the burden of treatment is one reason that PA is feared by people with CF and their families (Palser 2015). The use of prophylactic antibiotics, particularly nebulised, in people with established chronic PA can impact on school, work and social life (Conway 1996). As such, strong evidence as to the efficacy of long-term antibiotic treatment is essential before it can be advocated to people with CF. In the current financial climate it is also important to assess the cost-benefit of such potential treatments, particularly as the prognosis of people with CF continues to improve (Hurley 2014; Knibbs 2014).

We will therefore examine current evidence to assess the safety, tolerability and cost-effectiveness of secondary prevention strategies proposed to prevent recurrent PA infection in PWCF.

OBJECTIVES

To establish whether secondary prevention strategies, using antibiotics or other therapies, increase the chances of PWCF remaining free from PA infection following successful eradication therapy.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), published or unpublished and in any language will be included. Quasi-RCTs will be included if the authors are satisfied that the groups are similar at baseline.

Types of participants

People with CF, diagnosed clinically or by genetic or sweat testing. Each participant must have had an episode of PA within the last

six months which was successfully treated with an eradication regimen. They must remain free of infection with PA between the end of eradication and start of treatment for ongoing prevention.

Types of interventions

In PWCF in whom PA has been successfully eradicated, we will compare a time-limited course of therapy (if this is antimicrobial, it may be oral, inhaled or intravenous or any combination of these) to prevent a recurrent infection with the organism to usual care, placebo or another therapeutic strategy. Time-limited therapy will include all treatment in which a specific duration is pre-specified. Time-limited therapy will include regimens where the treatment is intermittent but continues at specified intervals for a defined duration. Long-term suppressive therapy, given for an indefinite period, will not be considered.

Types of outcome measures

Primary outcomes

1. Time to next isolation of PA (identified by any method, e.g. sputum culture, BAL or OP culture and as defined by the trial investigators)

Secondary outcomes

1. Change in quality of life (QoL) from baseline (as measured by a validated tool (e.g. the Cystic Fibrosis Questionnaire-Revised (CFQ-R) (Quittner 2009), the Cystic Fibrosis Quality of Life Questionnaire (CFQoL) (Gee 2000) or any other validated tool)
2. Change (absolute and relative) from baseline for pulmonary function tests
   a. forced expiratory volume in one second (FEV_1) measured in both L and % predicted
   b. forced vital capacity (FVC) measured in both L and % predicted
3. Pulmonary exacerbations
   a. time to next exacerbation
   b. frequency of exacerbations
   c. number of days in hospital
4. Nutritional parameters - change from baseline
   a. weight (kg) and weight centile or Z score
   b. height (cm) (children) and height centile or Z score
   c. body mass index (BMI) and BMI centile
5. Time to chronic PA infection (as defined by the trial investigators)
6. Adherence to treatment
   a. self-reported measures (e.g. participant diaries)
   b. secondary count measures (e.g. pill counting, days of intravenous antibiotics)
   c. electronic data (e.g. downloaded nebuliser data)
7. Adverse effects of treatment
   a. mild (self-limiting, not requiring treatment change, e.g. wheeze with inhaled therapy which settles
   b. moderate (requires treatment discontinuation, e.g. ototoxicity (damage to the ears causing hearing loss or balance problems))
   c. severe (e.g. hospitalisation or death)
8. Mortality
9. Isolation of resistant bacteria (with detection method, i.e. conventional culture or molecular techniques, described where possible)
   a. PA with a new resistance pattern
   b. methicillin-resistant *Staphylococcus aureus* (MRSA)
   c. resistant gram negative organisms (e.g. *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, *Achromobacter xylosoxidans*)
   d. other novel organisms
10. Cost effectiveness

Search methods for identification of studies

Electronic searches

The authors will identify relevant studies from the Group's Cystic Fibrosis Trials Register using the terms: (pseudomonas aeruginosa OR mixed infections) AND (eradication OR preventative OR unknown).

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant sections of the Cochrane Cystic Fibrosis and Genetic Disorders Group Module.

Searching other resources

Two authors (AA and SP) will independently analyse reference lists from all identified trials (whether included or not) to look for any previously unidentified trials. The trials databases International Standard Randomised Controlled Trials Number (ISRCTN) (www.isrctn.com/), clinicaltrials.gov (clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) database (www.who.int/ictrp/en/) will be searched using the terms (pseudomonas aeruginosa OR mixed infections) AND (cystic fibrosis) AND (eradicate OR eradication OR eradicating OR prevent OR prevention OR preventing OR preventative OR reoccurrence OR recur OR recurrent OR recurrence OR reoccur OR unknown). The authors will contact the chief investigator of any trials identified via these resources for any unpublished data.

Data collection and analysis

Selection of studies

Two authors (SP and AA) will independently screen the titles and abstracts of identified trials for inclusion in this review according to the processes set out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). They will exclude those trials which are obviously irrelevant and remove duplicates; where necessary, they will translate the full texts of the remaining trials into English. The two authors (SP and AA) will independently screen the identified trials against the review's eligibility criteria and collate multiple reports of the same trial where necessary. The authors will not be blind to the trial authors. They will resolve any disagreement by discussion and in consultation with the third

author (EN) where necessary. They will contact the corresponding trial investigator(s) if further information is necessary to decide whether to include a trial in the review.

Data extraction and management

Two authors will independently extract data using a data collection form which has been agreed by all authors. The data collection form will include information on the trial authors and eligibility, in addition to the trial methods (type of trial, blinding, setting, duration, number of centres and dropouts) and outcome data. For each trial, the authors will document the length of time after first isolation of PA and after successful eradication that a participant could be randomised. They will additionally record the active intervention (antibiotic type, route of administration, dose, duration) and the control intervention. Authors will consider all antibiotic regimens together initially and possibly undertake a subgroup analysis of administration route at a later date (see below). They will collect data on the participant demographics, including information on participants who dropped out.

The authors will collect data from the text, tables and online supplements where appropriate and resolve any disagreements by discussion. They plan to collect data at two weeks, one month, three months, six months and one and two years. If trials report data at other time points, the authors will consider examining these data as well; they will enter the information collected into the Review Manager software (RevMan 2014).

Assessment of risk of bias in included studies

Two authors (AA and SP) will independently assess the included trials for any risks of bias using the Cochrane's Risk of Bias tool described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). This tool facilitates the identification of bias in the following domains:

- random sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- incomplete outcome data;
- selective reporting;
- other bias.

The authors will review each trial and assess the risk of bias in each domain, classifying each as having a high, low or unclear risk of bias. If any disagreement occurs they will resolve this by discussion and seek the opinion of the third author (EN) where necessary.

Measures of treatment effect

For dichotomous outcomes, such as mortality and development of resistant bacteria, the review authors will seek data on the number of participants with each outcome and by allocated treatment group to allow an intention-to-treat analysis. They will calculate the risk of the outcome in treatment group compared to the risk of the outcome in the control group (pooled risk ratio (RR) and its 95% confidence interval (CI)).

For continuous data, such as change in QoL scores, pulmonary function tests and nutritional parameters, the authors plan to calculate the pooled mean difference (MD) and its 95% CI, between the intervention and control groups. Where the scales used differ, they will calculate the pooled standardised mean difference (SMD). They plan to report skewed data narratively.

The authors plan to analyse common count data (such as number of days in hospital) as continuous data, as described in the*Cochrane Handbook of Systematic Reviews of Interventions* (Deeks 2011).

For time-to-event data (such as time to next isolation of PA) the authors will calculate pooled hazard ratios and their 95% CIs.

Unit of analysis issues

The authors will not include any cross-over trials* as this is an inappropriate design for our review question. It is firstly unlikely that all participants would have fulfilled the primary outcome (time until a new growth of PA) at the point of cross-over; and secondly, once the outcome was reached cross-over would be meaningless. Cluster-randomised trials* are also inappropriate as there may be geographical differences between the PA strains which could affect eradication and re-acquisition rates. The authors will analyse factorial trials, where there is no suggestion of an interaction between the two interventions, separately (Higgins 2011c). Where a trial compares multiple treatment arms of interest these will be presented in separate comparisons. The authors will directly compare treatments of differing durations as each represents a separate treatment regimen.

* For definitions of these types of trial please see the Cochrane online glossary (https://community-archive.cochrane.org/glossary).

Dealing with missing data

Where possible, the authors will compare the outcomes proposed in the trial protocol to those in the published report. They will contact the trial authors or the sponsor for missing data. They will collect data on the number of participants with each outcome according to the allocated group, allowing an intention-to-treat analysis. Where necessary, the authors will use the methods described in Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* to impute these data (Higgins 2011a). If they need to impute significant amounts of data, they will undertake a sensitivity analysis to compare the effects of the imputed data against the available case data.

Assessment of heterogeneity

If the authors are able to undertake any meta-analyses, they will test for heterogeneity using the I^2 statistic, and interpret this according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). The authors note that the usefulness of I^2 depends on the magnitude and direction of the intervention effects and the strength of the evidence of heterogeneity. The authors will consider an I^2 value of 0% to 30% to represent little or no heterogeneity, 30% to 50% to represent moderate heterogeneity, 50% to 75% to represent substantial heterogeneity and above 75% to represent considerable heterogeneity.

Assessment of reporting biases

The authors aim to minimise the effects of reporting biases through a number of strategies. They will assess publication bias by a comprehensive search of grey literature and clinical trials databases, as well as by discussion with researchers in the field in an attempt to identify unpublished data; this will also help reduce

location and citation bias. The authors are, however, aware of the potential bias inherent in the inclusion of unpublished data. The inclusion of trials published in any language will reduce the risk of language and location bias. The authors will carefully screen trials at inclusion to look for evidence of duplicate publication, including author names, sites, interventions and participant characteristics. The authors will assess outcome reporting bias by the comparison of outcomes specified in the 'Methods' section to those reported in the results of the full trial paper. They will further investigate this bias by comparing the outcomes reported in the full paper to those stated in the protocol (if available). Where the trial protocol is unavailable, and if concerns remain, the review authors will contact the trial investigators to request a copy of the original trial protocol.

If the authors identify a sufficient number of trials (i.e. at least 10), they will construct funnel plots comparing trial effect to trial size. They will visually inspect these plots for evidence of asymmetry and, where appropriate, test for asymmetry as discussed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011). The review authors are aware that other causes of asymmetry in a funnel plot are possible and will consider the impact of these other factors.

Data synthesis

If sufficient trials are available to combine, the authors plan to assess the extracted data using a fixed-effect meta-analysis. In the case of substantial heterogeneity (I^2 greater than 50%), they will conduct a random-effects meta-analysis.

Subgroup analysis and investigation of heterogeneity

The authors will undertake the following subgroup analyses as appropriate:

- comparison of the effect of route of antibiotic administration (oral versus inhaled versus intravenous);
- comparison between participants who underwent eradication of a first episode of PA infection versus those with previous PA infection;
- comparison of differing methods of PA detection;
- comparison of differing definitions of recurrent PA infection;
- comparison of differing definitions of chronic PA infection.

Sensitivity analysis

If appropriate the authors will undertake a sensitivity analysis to ascertain whether the results of the review are robust. Authors will exclude trials assessed as having a high risk of bias (more than 50% of domains with a high risk) and repeat the analysis to see if this has any effect on the results. If the sensitivity analysis shows little difference, greater confidence can be placed in the results. Furthermore, in situations where the authors have made arbitrary decisions, such as the time points for analysis, or if they have imputed significant amounts of data, they will carry out a sensitivity analysis to assess the impact of these decisions. Once again similar results will strengthen the conclusions of this review, while conversely if there is a marked difference the review results will need to be interpreted more cautiously.

Summary of findings table

The authors will construct a summary of findings table for each comparison, for example antibiotic interventions, to prevent recurrence of PA infection following a period of eradication treatment in PWCF using the GRADEpro software. They will consider the following outcomes:

1. time to next isolation of PA;
2. QoL;
3. FEV_1 (change from baseline);
4. frequency of pulmonary exacerbations;
5. time to chronic PA infection;
6. adverse events; and
7. emergence of novel bacteria.

They will use the GRADE approach, described in Chapter 12 of *the Cochrane Handbook of Systematic Review for Interventions* (Schünemann 2011) to classify the body of evidence as high, moderate, low or very low. Where the authors judge the evidence not to be high quality, they will describe the rationale for this judgement in footnotes to the table. If, during the process of carrying out the review the authors identify further outcomes of interest, they will consider adding these to the table.

ACKNOWLEDGEMENTS

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Review stage: extract data from trials (2 people)	Dr Sally Palser Dr Edward Nash Arnav Agarwal
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Review stage: carry out the analysis	Dr Sally Palser
Review stage: interpret the analysis	Dr Sally Palser Dr Edward Nash Prof. Alan Smyth
Review stage: draft the final review	Dr Sally Palser Dr Edward Nash Prof. Alan Smyth
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Dr Edward Nash declares no known potential conflict of interest.

Dr Arnav Agarwal declares no known potential conflict of interest.

Prof Alan Smyth declares that he is on the advisory board for Vertex (produces CFTR modulators) and Gilead (manufacturers of inhaled antibiotics), has previously undertaken contracted research for Vertex, Raptor pharmaceuticals (manufacturers of inhaled antibiotics) and Insmed (manufacturers of inhaled antibiotics), has been paid for delivering a lecture by Gilead and co-wrote a paper which describes a Raptor trial.

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