Impact of treatment completion, intolerance and adverse events on health system costs in a randomised trial of 4 months rifampin or 9 months isoniazid for latent TB

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ABSTRACT

Rationale Treatment for latent tuberculosis infection with isoniazid for 9 months (9INH) has poor completion and serious adverse events, while treatment for 4 months with daily rifampin (4RIF) has significantly higher completion and fewer adverse events.

Objectives To compare the health system costs of 4RIF and 9INH.

Methods In a randomised trial conducted in five Canadian centres, one Brazilian and one Saudi Arabian centre, consenting subjects were randomised to receive 4RIF or 9INH. Health system costs were estimated from healthcare utilisation including scheduled and unscheduled visits, investigations and drugs. All activities for all subjects were evaluated using financial information from 2007 from the Montreal Chest Institute. Costs were expressed in Canadian dollars.

Results Total health system cost per patient allocated to 4RIF was $854 compared with $970 for 9INH ($p<0.0001$). The average cost per patient for the 328 of 420 (78%) who completed 4RIF therapy was $1094 compared with $1625 for the 254 of 427 (60%) completing 9INH ($p<0.0001$). Costs were modestly increased in patients with minor intolerance and substantially increased if the treating physician stopped treatment because of possible adverse events. Total costs related to management of adverse events with 9INH were $48 142 compared with $25 684 for 4RIF ($p=0.008$). Using these data, incremental cost-effectiveness analyses showed that 4RIF would be cost saving and prevent more cases within 2 years if efficacy exceeded 74%, and cost saving if efficacy exceeded 65%.

Conclusions The 4RIF regimen was significantly cheaper per patient completing treatment because of better completion and fewer adverse events.

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INTRODUCTION

Two billion of the world's population is estimated to have dormant or latent tuberculosis (TB) infection (LTBI). Of those infected, it is estimated that 9.2 million develop active TB each year, of whom 1.7 million die—the greatest cause of death from infectious disease after HIV,[1] despite the existence of effective treatment for LTBI.[2]

The currently recommended standard treatment for LTBI is a once-daily regimen of isoniazid taken for 9 months (9INH).[2 3] In the USA this is used to treat more than 80%[4] of the estimated 250 000 persons[5 6] who are prescribed LTBI treatment each year, as it has efficacy of 90%[7] if patients complete treatment. However, in routine practice, less than 50% of patients complete treatment,[8] substantially reducing the effectiveness of this approach. Treatment for 4 months with daily rifampin (4RIF) is a recommended alternative[2 3] for persons intolerant of INH or exposed to persons with INH-resistant TB. 4RIF has been shown to have significantly higher rates of completion and lower rates of hepatotoxicity than 9INH.[9–11] We have completed a multicentre randomised trial to compare the rate of serious adverse events, treatment completion and health system costs with 4RIF and 9INH. The findings with regard to treatment completion and adverse events have been reported elsewhere.[9] The comparison of costs and relationship of costs to these treatment outcomes is reported here.

METHODS

Study design and data gathering

An open-label randomised controlled trial was conducted at seven university-affiliated hospitals, five in Canada and one each in Saudi Arabia and Brazil. Eligible adults with a documented positive tuberculin skin test[3] whose treating physician had recommended treatment for LTBI signed informed consent. All patients were considered eligible unless they had absolute contraindications to the use of INH or RIF, regardless of risk factors for adverse events or non-compliance, as long as their treating physician believed that treatment of LTBI was indicated.

We wished to ascertain study outcomes and costs under routine conditions, so patients were followed by their usual treating physician who made all management decisions. If treatment was stopped by the treating physician because of a possible adverse event, these were reviewed by a three-member independent panel blinded to the study drug. Treatment outcomes were classified as:

Completed: if they took at least 80% of doses within 180 days for 4RIF and 365 days for 9INH. This group was subdivided into those who reported symptoms during follow-up (poor tolerance) and those who did not.

Default: patients who refused treatment, dropped out or took less than 80% of doses. This group was also subdivided into those who reported symptoms and those without symptoms.

Physician stopped treatment permanently: this group was classified by the independent review panel into grade 1–2 or grade 3–4 adverse events or not a drug-related adverse event.

Measuring and defining costs

We estimated direct costs from the perspective of the healthcare system. Healthcare utilisation of each study participant was recorded at all centres; these were divided into two categories of scheduled and non-scheduled care. Scheduled care included pretreatment and scheduled follow-up clinic visits, physician and pharmacist fees, nursing care, routine blood and radiological tests and TB medications. Non-scheduled care included walk-in clinic or emergency visits, treatment-related hospitalisations, additional nursing visits, investigations, speciality consultations and medications for adverse events. We did not include building or administration costs, patients' out-of-pocket expenses or their indirect costs related to time lost.

All activities (measured at all centres) were evaluated using financial information from 2006 to 2007 from the Montreal Chest Institute, Montreal, Canada. Physician and pharmacist activities and medication costs were based on reimbursement schedules of the Ministry of Health of Quebec effective in 2007 (see table S1 in online supplement). For secondary analyses, the same activities were assigned values using financial information obtained in July 2007 from the University Health Network Hospital, Toronto, Canada (by KK) and from the Brazilian Ministry of Health, Brazil (by AT) (see tables S2 and S3 in online supplement summarising the most important personnel, laboratory and medication costs for each site. Brazil costs were converted to $CAD: $1.00 CAD=1.73 Real).[12] In a separate analysis we varied only the cost of drugs based on the prices set by the Global Drug Facility.[13] This facility provides high-quality TB drugs, yet the prices for rifampin and isoniazid are 97% and 87% lower, respectively, than in Canadian pharmacies.

Cost comparison analysis

Costs were calculated as the product of the unit cost for each activity and the frequency of that activity. A 1-year analytical horizon was used, corresponding to the maximum time of treatment, so costs were not discounted.[14 15] Differences in costs between treatment groups (4RIF and 9INH) were tested for significance using Student t tests or ANOVA for normally distributed costs, otherwise Wilcoxon rank sum tests were used.[16] We estimated average treatment costs for each arm per patient randomised and per patient who completed treatment. Costs per month of treatment were calculated based on the total number of person-months of treatment.

All data were analysed using Stata Version 9.2 (Stata Corp, College Station, Texas, USA).

Cost-effectiveness analysis

We calculated an incremental cost-effectiveness ratio for treatment of newly infected close contacts with the two regimens using a 2-year analytical horizon. We assumed that 5% of these contacts would develop active TB over the next 2 years if untreated,[17 18] and that 9 months of treatment with isoniazid would have 90% efficacy[7] if completed properly. This meant that 0.5% of those completing 9INH (and 5% of those not completing 9INH) would develop active TB over the 2 years of the analysis. We also assumed that all patients were infected with strains that were sensitive to isoniazid and rifampin. The efficacy of 4RIF is presently unknown. In the base case analysis we assumed efficacy would be the same as 9INH (90%), but in sensitivity analysis varied this to as little as 60%. This minimum was selected because, in a randomised trial, 3 months of treatment with rifampin had efficacy of 63% in preventing active TB among subjects with LTBI and silicosis.[19] We calculated the expected cases over 2 years based on these efficacy assumptions and the observed completion of each regimen in the trial. The difference between the number of cases expected with each type of treatment and the number expected without any treatment was the estimated number of prevented cases within 2 years. The total costs observed in the trial were divided by this number to estimate the cost per case prevented for each regimen. We performed a two-way sensitivity analysis comparing both the cost and efficacy of 4RIF relative to 9INH in order to assess the robustness of the incremental cost-effectiveness ratio (ICER).[14] In this analysis we repeated the ICER calculation as we increased the total cost per patient on 4RIF in 5% increments from the observed value to 25% higher. At each of these cost values we estimated the ICER while decreasing in 5% decrements 4RIF efficacy through a range from 90% to 60%.

RESULTS

Between 27 April 2004 and 31 January 2007, treating physicians at participating centres recommended LTBI therapy to 1008 eligible patients. The results regarding patient characteristics and the outcomes of adherence and severe adverse events are reported elsewhere.[9] In brief, 60 screened patients were ineligible, 161 declined to participate and 847 were randomised. All baseline characteristics were similar in participants randomly assigned to the two regimens. Of the 420 randomised to 4RIF, 328 (78%) completed treatment compared with 255 (60%) of 427 patients allocated to 9INH. Grade 3–4 adverse events occurred in 17 (4%) of those randomised to 9INH compared with 7 (1.7%) of the 4RIF group (p=0.04). Grade 3–4 hepatotoxicity occurred in 16 (3.8%) vs 3 (0.7%) of those taking 9INH and 4RIF, respectively (p=0.003).[9]

Detailed healthcare utilisation and costs

As shown in table 1, total costs for 4RIF were $358 690 and for 9INH were $414 280. The largest components of costs for 4RIF were routine clinic visits (38%), drugs and pharmacy fees (30%), routine blood tests (7%) and non-scheduled care for evaluation and management of suspected adverse events (7%). For 9INH the different components accounted for different proportions: routine visits accounted for 57%, drugs and pharmacy charges 12%, routine testing 7% and unscheduled visits 12% of total costs. The total cost per patient allocated to 4RIF was $116 less than the total cost per patient allocated to 9INH. This reflected significantly lower average costs for scheduled and unscheduled care with 4RIF. The differences in cost between the two regimens were even greater when expressed per patient who completed treatment, reflecting the significantly better treatment completion with 4RIF. In secondary analyses, using health system costs from Toronto, total treatment costs of both regimens were very similar to Montreal treatment costs; when using Brazil health system costs, both regimens were much cheaper (4RIF: $323 vs 9INH: $425, p<0.0001). In both of these analyses, 4RIF remained the cheaper regimen (data not shown in tabular form). When the analysis was repeated using Montreal health system costs but the TB drug prices from the Global Drug Facility, 4RIF would have cost $658 per patient randomised compared with $934 for 9INH (p<0.0001).

Table 2 summarises the relationship between symptoms, treatment completion and costs. Of 328 patients completing

Table 1 Detailed healthcare utilisation and total costs of treatment with rifampin for 4 months (4RIF) vs isoniazid for 9 months (9INH) (all costs in Canadian $)

	4RIF			9INH			
	Total cost	Total per patient allocated	Total per patient completed	Total cost	Total per patient allocated	Total per patient completed	p Value*
Scheduled care							
Clinical visits							
Baseline	$68334			$69473			
MD±RN follow-up	$94177			$152842			
RN follow-up	$39611			$73005			
Subtotal clinical visits	$202122	$481	$616	$295320	$692	$1158	
Medication							
Pharmacy fees	$10373			$20251			
Drugs for LTBI	$94825			$25609			
Subtotal treatment of LTBI	$105198	$250	$321	$45860	$107	$180	
Investigations							
Complete blood count (CBC)	$11628			$11277			
Liver transaminases	$14057			$13681			
Subtotal investigations	$25684	$61	$78	$24958	$58	$98	
Subtotal: scheduled care	$333005	$792	$1015	$366138	$857	$1436	0.026
Non-scheduled care							
Clinical visits							
Emergency room visit	$179			$894			
Unscheduled clinic visit	$701			$1051			
Specialist consultation	$2937			$3247			
Visit to evaluate adverse events	$9415			$18691			
Telephone call	$46			$162			
Visit to perform blood tests	$725			$1670			
Subtotal clinical visits	$14003	$33	$43	$25715	$60	$101	
Subtotal treatment for side effects	$218	$1	$1	$226	$1	$1	
Investigations							
Additional CBC	$3635			$7726			
Additional liver transaminases	$4766			$10966			
Other investigations							
Blood chemistries	$844			$910			
Hepatitis serology	$256			$425			
Iron or coagulation profile	$233			$337			
Other blood tests	$280			$440			
Urinalysis	$21			$42			
Pulmonary function tests	$352			$440			
Procedures	$1027			$546			
Imaging	$50			$369			
Subtotal investigations	$11464	$27	$35	$22201	$52	$87	
Subtotal: non-scheduled care	$25685	$61	$79	$48142	$113	$189	0.008
Overall total costs	$358690	854	1094	$414280	$970	$1625	<0.0001

*Student t test comparing differences in costs per patient allocated to 4RIF vs 9INH. Differences in cost per patient completed greater, hence more significant. Total and subtotal costs normally distributed. Only three differences were tested.
9INH, isoniazid treatment for 9 months; LTBI, latent tuberculosis infection. 4RIF, rifampin treatment for 4 months

4RIF, 148 (45%) reported some symptoms during treatment phase follow-up compared with 17 of 68 (25%) who defaulted. The cost per patient and cost per patient-month were slightly higher in those with symptoms than in patients without symptoms, both in those who completed and those who defaulted. Among the 255 who completed 9INH, 136 (53%) reported some symptoms during treatment compared with 48 (36%) of the 133 who defaulted from 9INH. Costs per patient-month were slightly higher in those with symptoms than in those without symptoms in each of these categories.

The treating physician was sufficiently concerned about the possibility of an adverse event to permanently stop the study drug in 41 subjects receiving 9INH and 28 subjects receiving 4RIF (table 3). Total costs per subject with suspected adverse events ranged from $1215 for one patient with a drug interaction and $1143 for each of the 28 patients with hepatotoxic reactions to $554 per patient with gastrointestinal intolerance. Grade 3–4 serious adverse events were associated with average costs that were almost twice as high as the average cost for subjects with grade 1–2 adverse events. Using the results from table 3 and table S4 in the online supplement, unscheduled costs averaged $36 in patients who did not report any symptoms during follow-up, $65 in patients who reported minor symptoms, $366 in patients with grade 1–2 adverse events and $778 in patients with grade 3–4 adverse events. Costs for evaluation and management of specific adverse events averaged $1249 for

Table 2 Association of symptoms, adverse events and completion with costs (all costs in Canadian $)

	n	Costs for scheduled care	Costs for non-scheduled care	Total costs	Total costs per patient	Total costs per patient per month‡
(A) Results with 4RIF						
Completed therapy						
No symptoms or problems	180	$154153	$5278	$159431	$886	$219
Had symptoms but completed	148	$130031	$7139	$137170	$927	$232
Did not complete, default						
Never started*	2	$392	$0	$392	$196	–
Patient default, no symptoms	49	$21202	$237	$21339	$435	$279
Had symptoms, and patient defaulted	17	$9289	$1440	$10729	$631	$379
Drugs permanently stopped by physician†						
Drug-related adverse events	16	$4954	$7468	$12422	$776	$565
Pregnancy	1	$251	$233	$484	$484	$484
Not a drug-related adverse event	9	$2751	$3889	$6640	$738	$487
(B) Results with 9INH						
Completed therapy						
No symptoms or problems	119	$119297	$8344	$127641	$1073	$120
Had symptoms but completed	136	$142250	$11551	$153801	$1131	$126
Did not complete, default						
Never started*	5	$970	$0	$970	$194	–
Patient default, no symptoms	80	$37948	$1992	$39940	$499	$260
Had symptoms and patient defaulted	48	$28409	$1827	$30236	$630	$194
Study drug stopped permanently by physician†						
Drug-related adverse events	24	$8855	$17051	$25906	$1079	$357
Pregnancy or death	4	$1797	$1215	$3012	$753	$217
Not a drug-related adverse event	16	$7312	$6161	$13473	$842	$258

*Patients consented, were randomised, but then refused to start treatment. Costs are for baseline evaluation only.
†Final designation regarding whether drugs were stopped appropriately and severity/relationship to study drug were made by an independent panel, blinded to study drug.
‡Patient-months calculated from total number (sum) of patient-months on treatment within each group.
9INH, isoniazid treatment for 9 months; 4RIF, rifampin treatment for 4 months.

grade 3–4 adverse events compared with $668 for grade 1–2 adverse events (see table S4 in online supplement).

Cost-effectiveness analyses

As shown in figure 1, using the observed completion rates and costs for each regimen, the cost per case prevented within 2 years with 4RIF was substantially less than the cost per case prevented with 9INH if the efficacy of 4RIF was the same as 9INH. This difference in costs per case prevented between the regimens would decline if 4RIF had lower efficacy or higher costs. However, if 4RIF efficacy exceeds 75%, this would still prevent more cases and provide net cost savings compared with 9INH. If the efficacy of 4RIF was between 65% and 75%, then 4RIF would be cheaper but prevent fewer cases. 9INH would prevent more cases and would be less expensive only if the efficacy of 4RIF was below the threshold of 65%.

DISCUSSION

In this randomised trial, treatment of LTBI resulted in significantly lower health system costs per patient allocated to 4RIF than per patient allocated to 9INH. This was because of shorter treatment and fewer adverse events. The difference in cost per patient completing treatment was even greater because 78% completed 4RIF compared with only 60% completing 9INH. The efficacy of 4RIF is still undefined; however, if efficacy exceeds 65%, corresponding to the efficacy documented with 3 months' treatment with rifampin in one randomised trial,[19] then the regimen will be cost saving relative to 9INH. We would expect these cost savings to be generalisable given that completion rates in the trial were similar to those seen under normal practice conditions in other programmes (72%,[10] 74%[20] and 81%[11] with 4RIF and 53% with 9INH[10 11]).

Findings with 9INH in this trial reflect the major limitations of current LTBI treatment. 9INH is considered the regimen of first choice for LTBI because of its high efficacy.[7] However, in our trial and reports from several large programmes,[10 11 21] only 50–60% of patients who started 9INH completed the treatment, reducing the effectiveness of treatment to 50% or less. Although the medication is inexpensive, total costs for 9INH are high because close monitoring is required owing to the risk of drug-induced hepatitis. In this trial, hepatotoxicity accounted for 40% of patients whose treatment was permanently discontinued by their treating physicians and 57% of all non-scheduled costs in this group. Interestingly, almost one-third of patients in whom treatment was stopped for suspected INH hepatotoxicity were judged not to have this problem by the independent panel which was blinded to study drug. This reflects the heightened awareness and concern of treating physicians about INH hepatotoxicity.[22]

The significantly lower rate of hepatotoxicity with 4RIF is therefore a very important potential advantage, especially if this finding is confirmed with broader clinical experience. To date, rifampin monotherapy has been associated with a very low rate of hepatotoxicity among elderly Chinese men,[19] homeless persons in Boston,[23] adolescents in California[24] and a broad spectrum of patients in New Jersey[11] and Maryland.[10] Two important advantages of 4RIF—better completion and lower hepatotoxicity—therefore appear generalisable and should result in consistently lower costs for 4RIF in all settings. This experience is in marked contrast to experience with the 2-month rifampin-pyrazinamide regimen in which completion was only slightly better[25]

Table 3 Costs for patients in whom drugs were permanently discontinued because of suspected adverse events (all costs in Canadian $)

	n	Costs for scheduled care	Costs for non-scheduled care	Total costs	Average cost per patient	p Value*
Treatment regimen						
4RIF	28	$9667	$12232	$21899	$782	0.05
9INH	41	$15013	$24651	$39664	$967	
Type of adverse event						
Hepatotoxicity	28	$11063	$20942	$32005	$1143	<0.001
Haematological	4	$1271	$2694	$3965	$991	
Rash	17	$5219	$6230	$11449	$673	
Gastrointestinal intolerance	7	$1543	$2269	$3812	$545	
Drug interaction	1	$305	$911	$1216	$1216	
Other‡	12	$5280	$3837	$9117	$760	
Final designation†						
Grade 3–4 drug-related adverse event	24	$9317	$18668	$27985	$1166	<0.001
Grade 1–2 drug-related adverse event	16	$4493	$5850	$10343	$646	
Not a drug-related adverse event	29	$10870	$12364	$23234	$801	
All patients in whom drugs were stopped	69	$24680	$36883	$61563	$892	–

*p Value from one-way ANOVA for comparison of mean costs within subgroups.
†Final designation regarding severity and relationship to study drug were made by an independent panel, blinded to study drug.
‡Other reasons for referral to independent review panel were: pregnancy (n=5 of whom 1 later completed therapy), arthralgia (n=1), rheumatoid arthritis (n=1), fatigue (n=1), decreased libido (n=1), dengue fever (n=1), depression (n=1) and death (n=1). None of these was judged to be related to the study drug.
9INH, isoniazid treatment for 9 months; 4RIF, rifampin treatment for 4 months.

and costs were significantly higher than with 6–9 months of INH[26 27] owing to the greater toxicity and consequent need for closer follow-up with the 2-month regimen.[26 27] The advantage of lower hepatotoxicity with rifampin monotherapy would be lost if LTBI is treated with both isoniazid and rifampin for 3–4 months, as advocated by some.[28]

This study had a number of strengths. Most importantly, it was based on a randomised trial, ensuring balance of patient, health provider and centre characteristics that may profoundly influence costs. In contrast to many previous cost-effectiveness studies, no assumptions were made about care utilisation or outcomes. All outcomes were carefully ascertained in 847 subjects and costs were based on actual healthcare utilisation during follow-up. These patients were cared for by many providers in nine very different settings, enhancing generalisability of findings. The finding that 4RIF was significantly cheaper was true in all settings and did not change if we evaluated activities in different Canadian or Brazilian centres, used Canadian or international drug prices, or assumed a wide range of plausible efficacy. This provides evidence of the robustness of the findings.

Nevertheless, our study had limitations. Costs may have been overestimated due to the more intensive follow-up and greater attention to potential side effects. This is an inherent problem in any randomised trial, but should not have been different between the two regimens. We assumed that all latent infection was with pan-sensitive TB strains, overestimating the effectiveness of both regimens. However, this assumption would have overestimated the effectiveness of isoniazid to a greater extent than rifampin because initial isoniazid resistance is more common than rifampin resistance in the USA,[29] Canada[30] and many other countries.[31] An earlier analysis found that cost-effectiveness of 4RIF would increase relative to 9INH with a higher prevalence of isoniazid resistance.[32] Finally, patients' out-of-pocket expenses and time lost were not included in this analysis. However, these costs should have been higher for patients taking 9INH, given the significantly greater number of visits observed.

One potential risk of 4RIF is the creation of rifampin mono-resistance. A recent meta-analysis[33] concluded that the risk of isoniazid resistance was modestly increased by isoniazid treatment of LTBI. Although this may simply reflect inadvertent monotherapy of unrecognised active TB, this risk is important because of the serious therapeutic implications of acquired rifampin resistance.[34] However, rifampin mono-resistance following 4RIF has not been reported in trials,[19] programme reports,[10 11] case series[23 24] or in surveillance reports even though 4RIF is used to treat approximately 4% of all patients with LTBI in the USA.[4] Nevertheless, it is important to maintain careful surveillance for the occurrence of this complication under routine programme conditions or in randomised trials.

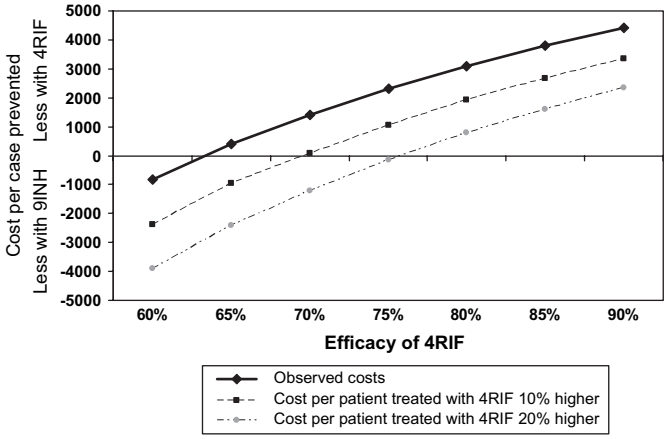

Figure 1 Difference in estimated cost per case prevented between rifampin taken for 4 months (4RIF) and isoniazid taken for 9 months (9INH). A value greater than zero means that the cost per case prevented with 4RIF was less than the cost per case prevented with 9INH. Solid line with diamonds represents analysis using observed costs with 4RIF and 9INH. Dashed line with squares represents total costs per patient randomised to 4RIF 10% more expensive than in base case analysis. Dashed and dotted line with circles represents total costs per patient randomised to 4RIF 20% more expensive than in base case analysis.

Our results may inform efforts for TB prevention. In the USA it has been estimated that 290 000–433 000 persons start treatment for LTBI,[5 6] of whom more than 80% take 9INH.[4] Based on estimates from this study, if all persons now taking 9INH were given 4RIF, this could result in savings of $22–33 million, even without considering the benefit of better completion. Potential savings from a switch to 4RIF would also be substantial in Canada, given that more than $25 million is spent annually on LTBI management.[35] The medication cost for rifampin in Canada and in the USA is many times higher than the costs of the Global Drug Facility.[12] If the same quality-assured rifampin[12] was available in the USA, savings with use of 4RIF could be as much as $66–98 million.

Better safety and improved completion rates are important reasons to consider the expanded use of the 4RIF regimen. Our study adds the advantage of significantly lower costs. We predict this regimen will be cost-effective if efficacy exceeds 65%. A multicentre trial involving over 6000 subjects in seven countries to assess the efficacy of 4RIF is now underway.

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Competing interest None.

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