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### Outpatient HIV care in the Netherlands

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# 6

## **Patients' willingness to take multiple-tablet antiretroviral therapy regimens for treatment of HIV**

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## **Abstract**

### **Background**

The costs of combination antiretroviral therapy (cART) for HIV, consisting of separate, particularly generic, components (multiple-tablet regimens, MTR) are generally much lower than those of single-tablet regimens (STR) comprising the same active ingredients.

### **Objectives**

To assess whether patients would be willing to take MTR, once-daily, instead of STR, with the goal of reducing general healthcare costs. In addition, we aimed to examine whether willingness was associated with particular patient characteristics.

### **Methods**

Data from the ATHENA cohort database in the Netherlands of adult HIV-1-infected patients in care and taking cART  $\geq 6$  months were used to select 1000 potential participants for an online patient survey on patient preferences and satisfaction. Participants were asked whether they would be willing to take three pills with the equivalent active ingredients simultaneously instead of STR to reduce costs. Multivariate logistic regression was used to examine associations between patient characteristics and willingness to take MTR instead of STR.

## **6**

### **Results**

Forty-seven percent ( $n=152$ ) of the 322 respondents answered 'yes' and 2% ( $n=83$ ) answered 'maybe' when asked whether they would be willing to take three pills with the equivalent active ingredients simultaneously to reduce costs. Non-Dutch patients were significantly more likely to answer 'no' (OR: 2.49; 95% CI: 1.17–5.30) or 'maybe' (OR: 2.63; 95% CI: 1.24–5.60). Answering 'no' was less common among patients who had been taking cART  $\geq 15$  years (OR: 0.23; 95% CI: 0.09–0.58). Commonly reported concerns included the dosing frequency, efficacy and tolerability of MTR.

### **Conclusion**

HIV-infected patients do not necessarily oppose the decision to prescribe MTR instead of STR to reduce healthcare costs. However, the potential trade-off in terms of convenience should be carefully weighed against the projected savings.

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## Introduction

The development of combination antiretroviral therapy (cART) has led to remarkable improvements in life expectancy and quality of life for those infected with human immunodeficiency virus (HIV).<sup>1</sup> Not only are cART regimens increasingly potent, they have also been greatly simplified. Regimens have evolved from combinations involving more than 20 pills taken several times per day to co-formulated drugs, taken once or twice daily.<sup>2</sup> Currently, the use of single-tablet regimens (STR), in which all components of a cART regimen are combined into a single tablet administered once daily, is widely recommended as first-line therapy.<sup>3</sup>

In contrast to these developments, there has been a recent shift towards the use of non-co-formulated cART generics in the form of multiple-tablet regimens (MTR). These MTR are less expensive than branded STR combinations. In a pharmaco-economic analysis, Walensky et al.<sup>4</sup> demonstrated that a switch from STR (efavirenz/emtricitabine–tenofovir) to MTR (generic efavirenz, generic lamivudine and tenofovir) in the USA would save nearly US\$1 billion in the first year. Another study in the UK showed that switching all patients to available generics could save an estimated £1.1 billion in 5 years.<sup>5</sup>

While the range of available generics, and therefore the options for saving costs through MTR, is expanding, it is unclear to what extent switching to MTR would affect adherence and virological outcomes.<sup>6</sup> Despite the considerable amount of evidence supporting the positive impact of a lower pill burden (number of pills) and dosing frequency on adherence,<sup>7–9</sup> few clinical data support the superior effectiveness of STR versus its separate components.<sup>3</sup> Indeed, there is evidence suggesting that STR and once-daily MTR are equally effective.<sup>10</sup> In recent studies evaluating the impact of cost-saving policies, switching to MTR did not affect clinical outcomes.<sup>3,11,12</sup> Additional studies supporting equivalence of STR and MTR include a meta-analysis of 19 RCTs<sup>13</sup> and a prospective cohort study<sup>14</sup> in which a lower pill burden in once-daily regimens did not predict better adherence.

The above-mentioned studies have provided evidence of cost savings and equivalent efficacy, but have not evaluated patients' attitudes towards taking MTR. Therefore, we assessed whether patients in the Netherlands would be willing to take MTR, once daily, instead of STR with the goal of reducing costs. In addition, we aimed to identify patient characteristics potentially associated with willingness to take MTR.

## Methods

### Study population

In The Netherlands, all HIV-infected patients are treated in designated HIV treatment centres, and prospectively monitored in the 'AIDS therapy evaluation in the Netherlands' (ATHENA) cohort (maintained by Stichting HIV Monitoring, SHM).<sup>15</sup>

We selected 1,000 HIV-1-infected patients from all treatment centres for participation in a larger study (Q-HIV) in which we assessed patients' health-related quality of life and perspectives on outpatient HIV care. The treatment centre size was taken into account, ensuring a minimum of 20 potential participants per treatment centre. We selected chronically infected patients with: (1) time since initiation of cART  $\geq 6$  months; and (2) age  $\geq 18$  years at the time of diagnosis. For the selection, we used the anonymized study ID number assigned to each HIV patient in care by SHM.

Selected potential participants were provided with an information letter and a password for accessing an online questionnaire in Dutch or English. We also offered a paper version of the questionnaire. The study was exempted from written informed consent (by the Medical Ethics Review Committee of the Academic Medical Centre of the University of Amsterdam); we considered consent implicit when a questionnaire was returned to us.

### Outcome measures

The participants were asked as follows whether they would be willing to take an MTR (once daily) instead of an STR to reduce costs:

*"The costs of medication are being critically assessed worldwide. The costs of 3 separate pills are generally much lower than the cost of a combination drug with the same active ingredients. Would you be willing to take 3 pills at the same time instead of 1 pill?"*

Respondents could answer 'yes', 'no' or 'maybe'. In addition, patients were given the opportunity to comment on the matter ("*Please fill in your comment here:...*"). We assessed the comments per group ('yes', 'no' or 'maybe').

### Patient characteristics

We used the ATHENA cohort database to extract the patient characteristics of age, sex, region of origin, socioeconomic status (SES), route of HIV transmission, time since cART initiation and time since diagnosis. Region of origin was based on the country of birth and grouped into the Netherlands, sub-Saharan Africa (SSA) and 'other'. For the SES we used a classification system previously described by The Netherlands Institute for Social Research.<sup>16</sup> Here, the five classes, based on area codes, were recoded as high, middle or low. Route of transmission was categorized as men who have sex with men (MSM), heterosexual contact or 'other/unknown'.

### Statistical analysis

We used t-tests, Mann–Whitney U tests and  $\chi^2$  analysis to test for differences in characteristics between respondents and non-respondents. Then, we stratified the proportions of respondents answering 'yes', 'no' or 'maybe' according to characteristics, and used  $\chi^2$  analysis to determine statistically significant differences in proportions between groups.

Using multinomial logistic regression, we assessed potential associations between patient characteristics and answering the question with 'yes', 'no' or 'maybe'. In this analysis, which accommodates three outcomes, we estimated the odds of answering 'no' versus 'yes' and the odds of answering 'maybe' versus 'yes'. We recoded region of origin as either from the Netherlands (Dutch) or 'other' (non-Dutch), and combined sex and transmission route (MSM, heterosexual male, heterosexual female and 'other'). Variables with  $p$  values  $<0.1$  in the univariate analysis were entered in a multivariate model. All analyses were performed with STATA (version 13).

## Results

Of the 1000 selected patients, 958 patients were eligible for participation (i.e. had not recently died, migrated or switched to another treatment centre). A total of 331 patients from all HIV treatment centres in the Netherlands completed the questionnaire (response rate: 35%) and 322 answered the question regarding switching to MTR. Twenty-five percent of respondents chose to complete the paper version of the questionnaire.

The proportions of males (85%), patients originating from the Netherlands (77%) and MSM (71%) were significantly higher among respondents than among non-respondents (73, 50 and 48%, respectively). Respondents were significantly older than non-respondents (average of 51 vs. 47 years) and had a higher SES. The groups did not differ with regard to duration of HIV infection or time since cART initiation. Of the 322 respondents, 47% ( $n=152$ ) answered 'yes', 27% ( $n=87$ ) answered 'no' and 26% ( $n=83$ ) answered 'maybe' when asked whether they would be willing to use an MTR to reduce costs. Table 1 shows the proportions of respondents answering this question with 'yes', 'no' or 'maybe' according to patient characteristics. An affirmative answer was relatively more common among older patients, men, Dutch patients, MSM and patients with a time since diagnosis or cART initiation of  $\geq 15$  years. Female respondents and respondents from SSA were most likely to answer the question with 'maybe'. Finally, patients taking MTR were more likely to answer the question with 'yes'.

### Respondents Answering 'Yes', 'No' or 'Maybe'

Table 2 shows the odds of respondents answering 'no' versus 'yes' and 'maybe' versus 'yes'. In the multivariate analyses, non-Dutch patients were significantly more likely to answer 'no' (OR: 2.49; 95% CI: 1.17–5.30) or 'maybe' (OR: 2.63; 95% CI: 1.24–5.60). Answering the question with 'no' was less common among patients who had been taking cART  $\geq 15$  years (OR: 0.23; 95% CI: 0.09–0.58).

### Views and Concerns

A total of 105 patients expressed their views in the comment field. Respondents reported that they would consider switching to MTR a step backwards ( $n=24$ ) and emphasized the importance of taking the pills once daily ( $n=6$ ).

## Chapter 6. Multiple pills

Table 1. Characteristics of respondents answering “yes”, “no” or “maybe” to the question whether they would be willing to switch from a single drug regimen to multiple pills (once daily) for the treatment of HIV.

Characteristic	YES		NO		MAYBE		p value
	n=152	(47%)	n=87	(27%)	n=83	(26%)	
Age (years)							0.046
<40	19	(37%)	21	(41%)	11	(22%)	
40–50	43	(43%)	32	(31%)	27	(26%)	
50–60	53	(53%)	17	(17%)	30	(30%)	
≥60	37	(54%)	17	(24%)	15	(22%)	
Sex							0.009
Male	139	(50%)	73	(27%)	64	(23%)	
Female	13	(28%)	14	(31%)	19	(41%)	
Region of origin							<0.001
the Netherlands	133	(53%)	61	(24%)	58	(23%)	
sub-Saharan Africa	1	(4%)	9	(38%)	14	(58%)	
Other	18	(39%)	17	(37%)	11	(24%)	
Socioeconomic status							0.087
High	47	(52%)	22	(24%)	22	(24%)	
Middle	56	(51%)	23	(20%)	32	(29%)	
Low	46	(41%)	41	(37%)	25	(22%)	
Missing <sup>a</sup>	3	(38%)	1	(12%)	4	(50%)	
Route of HIV transmission							0.027
MSM	123	(53%)	58	(25%)	52	(22%)	
Heterosexual	24	(33%)	24	(33%)	25	(34%)	
Other/Unknown	5	(30%)	5	(35%)	6	(35%)	
Time since cART initiation (years)							0.002
<5	32	(40%)	29	(36%)	19	(24%)	
5–10	46	(47%)	28	(29%)	23	(24%)	
10–15	25	(35%)	20	(28%)	26	(37%)	
≥15	49	(67%)	10	(13%)	15	(20%)	
Time since diagnosis (years)							0.011
<5	17	(45%)	10	(26%)	11	(29%)	
5–10	46	(43%)	38	(36%)	23	(21%)	
10–15	34	(39%)	26	(29%)	28	(32%)	
≥15	55	(62%)	13	(15%)	21	(23%)	
Currently on STR							<0.001
No	134	(58%)	35	(15%)	59	(26%)	
Yes	18	(19%)	52	(55%)	24	(26%)	

Abbreviations: cART, combination antiretroviral therapy; MSM, men who have sex with men; STR, single-tablet regimen.

p values for the comparison of characteristics ( $\chi^2$  analysis).

<sup>a</sup> ‘Missing’ group not included in analysis.

Four patients felt that the high STR prices were driven by the pharmaceutical industry and indicated that pricing is a political matter. Respondents who answered ‘maybe’ pointed out that potency and tolerability of the regimen should not be inferior to STR (n=5). Having to pay for medication was reported as a reason to consider switching to an MTR (n=3). The most common view of respondents who answered ‘no’ was that STR are more convenient, particularly when travelling or at work (n=8).

Table 2. Univariate and multivariate multinomial logistic regression analysis for respondents answering “no”, or “maybe” versus “yes” to the question whether they would be willing to switch from a single-drug regimen to multiple pills (once daily) for the treatment of HIV.

Characteristic	NO vs. YES		MAYBE vs. YES	
	Univariate OR (95% CI)	Multivariate OR (95% CI)	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age (years)				
<40	1	1	1	1
40–50	0.67 (0.31,1.46)	1.05 (0.45,2.45)	1.08 (0.45,2.63)	1.56 (0.59,4.11)
50–60	0.29**(0.13,0.66)	0.61 (0.24,1.56)	0.98 (0.41,2.33)	1.83 (0.67,5.01)
≥60	0.42*(0.18,0.97)	0.90 (0.34,2.36)	0.70 (0.27,1.82)	1.26 (0.42,3.74)
Sex and route of transmission				
MSM	1	1	1	1
Heterosexual, male	1.77 (0.72,4.33)	1.60 (0.60,4.25)	1.97 (0.80,4.85)	1.66 (0.62,4.47)
Heterosexual, female	2.47*(1.08,5.68)	1.90 (0.74,4.91)	2.96*(1.30,6.75)	2.54 (1.00,6.47)
Other	2.12 (0.59,7.61)	1.52 (0.37,6.24)	2.84 (0.83,9.71)	2.16 (0.54,8.61)
Region of origin				
the Netherlands	1	1	1	1
Other	2.98**(1.53,5.80)	2.49*(1.17,5.30)	3.02**(1.54,5.91)	2.63*(1.24,5.60)
Socioeconomic status				
High	1	1	1	1
Middle	0.88 (0.44,1.77)	0.79 (0.37,1.70)	1.22 (0.63,2.38)	0.98 (0.47,2.03)
Low	1.90 (0.99,3.68)	1.72 (0.84,3.54)	1.16 (0.58,2.34)	1.02 (0.48,2.17)
Time since cART initiation (years)				
<5	1	1	1	1
5–10	0.67 (0.34,1.34)	0.59 (0.28,1.22)	0.84 (0.40,1.79)	0.81 (0.37,1.79)
10–15	0.88 (0.41,1.91)	0.98 (0.42,2.30)	1.75 (0.80,3.86)	1.59 (0.67,3.81)
≥15	0.23**(0.10,0.52)	0.23**(0.09,0.58)	0.52 (0.23,1.16)	0.42 (0.17,1.02)
Time since HIV diagnosis (years) <sup>a</sup>				
<5	1	–	1	–
5–10	1.40 (0.58,3.42)	–	0.77 (0.31,1.92)	–
10–15	1.30 (0.51,3.31)	–	1.27 (0.51,3.16)	–
≥15	0.40 (0.15,1.08)	–	0.59 (0.24,1.47)	–

Abbreviations: cART, combination antiretroviral therapy; MSM, men who have sex with men;

\* p<0.05, \*\* p<0.01, \*\*\* p<0.001.

<sup>a</sup>Time since diagnosis was not included in the multivariate model because of collinearity (time since cART initiation).

Other reasons for reluctance included difficulties swallowing pills (n=4), increased risk of dosage errors (n=3), concerns about perceiving oneself as more ill (n=3) and concerns about side effects (n=2).



### Discussion

With the growing availability of generic antiretroviral agents, switching from STR to MTR is widely being considered as a strategy to reduce healthcare costs. In some settings, this switch has been structurally implemented.<sup>3,11,12</sup> The decision to take this measure, which is intuitively paradoxical to the simplification of cART regimens, must be preceded by an assessment of the efficacy of STR versus MTR, estimated savings and patient preferences.

Our study suggests that a considerable proportion of HIV-infected patients in the Netherlands would consider switching to MTR for economic reasons. Almost half the respondents answered 'yes' and a quarter answered 'maybe' when asked whether they would be willing to take MTR. Our results show that patients' willingness to switch to MTR is to some extent dependent on how long they have been taking cART. Patients who had been taking cART  $\geq 15$  years were more willing to take MTR, possibly because they experienced the years in which cART regimens were far more complex. Conversely, non-Dutch respondents were less willing to take MTR. A possible explanation for this could be that non-Dutch patients are more likely to have disclosure concerns, as reported in a previous study among HIV-infected patients in the Netherlands.<sup>17</sup> Patients preferring not to disclose their HIV serostatus report more medication hiding,<sup>18,19</sup> and hiding medication may be perceived as easier with STR.

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Our qualitative results show that patients (including respondents willing to switch) feel that switching to MTR is a step backwards. In addition, the most common concerns appear to be the dosing frequency, efficacy and tolerability of MTR. Thus, these matters deserve attention in both decision making and in informing the patient regarding MTR.

### Strengths and limitations

We consider the fact that we have data from all the treatment centres in the country to be a strength of this study. Furthermore, we offered the option of completing out a paper version of the questionnaire, to reduce sampling bias that can occur when collecting patient-reported data online.<sup>20</sup> Finally, the open-ended nature in which respondents could state their views and concerns provided us with a variety of information that we could not have anticipated had we chosen to offer a limited number of answers. Despite efforts to recruit a nationally representative sample of individuals with HIV, patients from the Netherlands, MSM and patients with a higher SES were over-represented in our study sample, possibly resulting in a higher overall percentage of willingness to switch. Another limitation is the hypothetical character of our question (limited to 'once-daily' dosage), with responses possibly not predictive for willingness in a real-life setting. In addition, given our aim to assess views in a cross-section of the HIV population, we posed the question to patients who were not on single-drug regimens at the time of participation. The response of those on STR (19% willing to switch) and those on MTR (59% willing to switch) may need to be interpreted differently. On the one hand, the individuals of concern in this matter (i.e. those on STR) have a strong preference for STR.

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On the other hand, one could argue that experience with multiple pills is not discouraging to the extent that, when given the (hypothetical) choice, patients would be reluctant to switch to MTR.

With regard to the generalizability of our results, it is important to bear in mind that in the Netherlands, where all citizens are legally required to be insured, there is universal access to cART (without co-payment). In settings where this is not the case, individual financial factors are likely to play to an important role in patients' positions regarding this matter.

### **Implications**

This exploratory study shows that patients' preferences are not necessarily a reason to disregard the option of prescribing MTR. Our results suggest that, if well informed about the efficacy and tolerability, patients may find switching to MTR for economic reasons acceptable.

In particular, our results suggest that patients from the Netherlands and patients who have been taking cART for  $\geq 15$  years (a substantial proportion of the HIV-infected population in The Netherlands) may be more likely to approve a switch to MTR. For patients more reluctant to switch, further inquiry into the concerns they may have is important. Our results suggest that these may include potency, tolerability, inconvenience and swallowing difficulties. Other issues to cover in clinical practice will differ per setting and include the financial consequences for the individual patient, the option to switch back to STR and dosing frequency.

### **Conclusion**

HIV-infected patients do not necessarily oppose the decision to prescribe MTR instead of STR to reduce healthcare costs. However, the potential trade-off in terms of convenience should be carefully weighed against the projected savings. Moreover, considering the scarcity of evidence on the efficacy and safety of switching to MTR,<sup>3,13</sup> outcomes of such switches should be closely monitored over the long term.

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