Structured medicines reviews in HIV outpatients: a feasibility study (The MOR Study)

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Title: Structured Medicines Reviews in HIV outpatients: a randomised controlled trial (The MOR Study)

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Abstract:

Objectives: Polypharmacy in people living with HIV (PLWH) increases the risks of medicine-related problems (MRPs). We aimed to examine the feasibility and acceptability of a Medicines Management Optimisation Review (MOR) toolkit in HIV outpatients.

Methods: Multicentred randomised controlled study across 4 HIV centres. 200 PLWH on cART, either over 50 years old or under 50 years with other comorbidities, were enrolled to have a MOR or received standard pharmaceutical care. The primary outcome was the difference in the number of MRPs between intervention and standard of care groups at baseline and 6 months. Acceptability, cost of the intervention and health related quality of life were also examined.

Results: 164 patients were analysed: 70 in the intervention group and 94 in the standard of care group. A significant number of MRPs were detected in those patients receiving MOR compared to standard of care group at baseline [93 vs 2; (p=0.001; z=-8.6; r: 0.6)] and 6 months [33 vs 3; (p=0.001; z=-5.7; r=0.4)]. A significant reduction in the number of new MRPs at 6 months in the intervention group compared to baseline was also observed (p=0.001; Z=-3.7; r:0.2). 44% of MRPs were fully resolved at baseline and 51% at 6 months. No changes in health-related quality of life following MOR or between MOR and standard of care groups were observed. MORs were highly acceptable among patients and health care professionals.

Conclusions: MOR toolkit was feasible and acceptable suggesting HIV outpatient services might consider implementing MOR for targeted populations under their care.
The introduction of combination antiretroviral therapy (cART) has transformed HIV disease from a life-threatening illness into a chronic condition with near-normal life expectancy, with the majority of people living with HIV (PLWH) in the UK expected to be over 50 years of age, by 2025 (1). The synergistic effects of HIV and ageing predispose patients to higher levels of co-morbidities at younger ages compared to the general population (2) consequently, polypharmacy and medicine related problems (MRPs) are an important challenge facing older PLWH and their care providers (3-5). In the general population older age, multiple comorbidities and polypharmacy are significantly associated with adverse drug events, drug-drug interactions (DDIs) and low adherence to medications (6). MRPs also cause greater health care resource utilisation, leading to significantly higher healthcare costs (7). Older PLWH are at particular risk of MRPs because on average they have more comorbidities and are prescribed more medicines than those who are younger or than people who are HIV-negative (8, 9). Moreover, treatment of PLWH with cART is complex, with significant propensity for MRPs (10). MRPs, where medicines are either prescribed inappropriately, or the intended benefits are not realised have also been identified globally as significant contributory factors to medicine-related harm (11, 12), with higher prevalence of preventable medication harm observed in older people (13).

There is extensive evidence in older people with multimorbidity that medicines optimisation, including Structured medicine (or medication) reviews (SMRs), contributes to reducing the incidence of MRPs (14). Availability of complete medicines lists has been shown to reduce number of DDIs per HIV outpatient (15), and a specialist pharmacist consultation prior to routine HIV outpatient appointments has been shown to increase detection of potential DDIs (16). Hence medication reviews are one of the medicines optimisation tools recommended to reduce the risk of DDIs and other MRPs in PLWH. However, despite the well-documented higher prevalence of DDIs and polypharmacy in PLWH, evidence of the benefits of medication reviews in the HIV outpatient setting is lacking.
We aimed to examine the feasibility and acceptability of a Medicines Management Optimization Review (MOR) toolkit and the impact of the intervention on health-related quality of life and costs.

Methods

Study design and participants
We conducted a randomised controlled open trial between January 2018 and December 2019. In total, 200 participants were recruited from four HIV outpatient clinics within the Sussex HIV Network (Brighton, Chichester, Crawley, and Worthing). Inclusion criteria were PLWH over 18 years of age prescribed cART, with participants required to be either over 50 years of age or under 50 years with comorbidities for which the participant was prescribed at least one regular medicine. Patients who had received a recent medicines review by an HIV pharmacist as part of their routine care within the previous 6 months were excluded.

Patients were recruited while attending clinic for a routine appointment. Following receipt of participant consent and questionnaire completion, 1:1 block randomisation was conducted using Sealed Envelope (17). 100 participants were randomised to receive the intervention (a structured medicine review using the MOR toolkit), while 100 controls received standard HIV outpatient pharmaceutical care. Participants in the intervention arm underwent the MOR with an HIV pharmacist within 1 month of consent and again at 6-8 months from consent, with MOR appointments scheduled as close as possible to the participants’ routine 6 monthly blood test or medical appointments. Control arm participants received standard pharmaceutical care following their 6 monthly medical appointments. See figure 1 for study flow chart.

Intervention:
The Medicines Optimisation Review (MOR) toolkit was collaboratively developed in 2014 by four UK-based HIV specialist pharmacists, with project management and logistical support from Wave Healthcare Communications (an independent medical education agency). The initiative was facilitated and funded by Merck Sharp & Dome (MSD) UK and the toolkit is endorsed by the UK HIV Pharmacy Association (HIVPA). The core objective of the toolkit is to enhance patient safety by identifying and reviewing all patients at a higher risk for
polypharmacy or DDIs in an HIV outpatient setting. The toolkit comprises a user guide and a
supply of two forms: ‘My Clinic Companion’ and ‘MOR consultation form’ (Supplementary
data Figure 1). ‘My Clinic Companion’ (Supplementary data Figure 1a) is a patient-orientated
questionnaire that promotes the self-review of medications and adherence; it can be used
both to identify patients who are most likely to benefit from a MOR appointment and to
facilitate the structured medication review. The ‘MOR consultation form’ (Supplementary
data Figure 1b) is designed to aid, and provide a record of, the structured patient consultation
using information derived directly from the patient and, where necessary, primary care
prescribing records and information from local databases (e.g. hospital records). In addition,
the ‘MOR consultation form’ identifies any key care providers who may be involved with the
patients’ health care including prior consent to contact if this is required and identifies health
care interventions which may be beneficial to the patient such as smoking cessation or
adherence education.

Standard of care
An HIV specialist pharmacist conducts a “clinical screen” of the cART prescription in the clinic
before the patient takes it to the hospital outpatient pharmacy for dispensing. This includes
viewing the electronic patient record to verify the drugs and doses prescribed, check relevant
blood test results and documented concomitant medications (“comedications”), as well as
asking the patient if they are taking any new medicines or have any questions.

Data collection:
Demographic and clinical data were recorded for all participants following consent (age,
gender, ethnicity, sexuality, age at HIV diagnosis, years on cART, type of cART regimen,
current CD4, nadir CD4, HIV RNA viral load, number of comorbidities, and number and type
of comediations). MRPs were categorised as: potential adverse reactions; potential drug-
drug interaction (DDI) with cART, identified using the University of Liverpool and/or Canadian
HIV drug interactions references (18, 19); dose adjustment required; problems with handling
or administration; off-label drugs used inappropriately; under-treatment (no prescription for
an actual indication according to medical guidelines), and unnecessary drugs which could
safely be stopped or simplified. The duration of the consultation and time spent preparing
the pharmacist’s report was also recorded as well as their recommendations (to be resolved by the patient, GP or consultant HIV physician) resulting from the MOR consultation.

**Patient and healthcare provider satisfaction:**

A voluntary self-completed survey was given to participants after the follow up MOR clinic appointment. The survey asked participants to rate the MOR service provided by the pharmacist and whether they felt more confident managing their medicines after the review. An online questionnaire for health care professionals working in the HIV clinics (excluding those providing the MOR service) was accessible from December 2019 to March 2020. This was created and hosted using Online Surveys (20) and distributed via email to HIV clinical staff. Job role, perceived importance of the service and improvement to PLWH care were assessed. Partially completed questionnaires were omitted from analysis.

**Intervention costs and health related quality of life**

Assessment of health-related quality of life was carried out using the EuroQol five-dimension five-level (EQ-5D-5L) questionnaire using the visual analogue scale (EQ-VAS). The visual analogue scale records the respondent’s self-rated health from 0 (“the worst health you can imagine”) to 100 (“the best health you can imagine”). The intervention was costed from the NHS perspective using the recommended methods for economic evaluations in health care (21). Costs associated with the medication review were estimated based on the times spent by pharmacists on main review activities including: arranging appointment with patients; meetings with patients; checking primary care prescribing (Summary Care Record) via the NHS spine portal; communicating with health care professionals with respect to the medication review; producing the medication review report; and any additional relevant documentation (eg adverse drug reaction reporting). Data on the time spent on these activities were collected prospectively using a purpose-designed resource use questionnaire (supplementary data). Data collected for each pharmacist included: the number of patients with whom they conducted a MOR; the number of MOR-related activities and the time spent on them (average, minimum and maximum time); as well as their pay band and HIV clinic site. Pharmacists’ time was calculated using the midpoint salaries of the UK NHS Agenda for Change pay scales 2018-2019 (22). The intervention costs were calculated per medication
review and per patient. Cost ranges were estimated using the maximum and minimum time spent on different review activities.

**Statistical analysis**

The primary endpoint of the study was change in the number of MRPs between the intervention group and control group at baseline and 6 months. All participants who were enrolled and subsequently baselined into the study formed part of the statistical analysis. All descriptive statistics of the quantitative data are presented with point estimates and indication of variability in data, where hyper-geometric distributed data are presented as a median with an inter-quartile range and Gaussian normal data are presented as a mean with a standard deviation. Change in the number of MRPs and EQ-VAS scores between intervention and control groups were calculated using Mann-Whitney. Within-study time point changes from baseline for non-parametric data were analysed using the Wilcoxon signed rank test. All statistical analyses were performed using SAS version 9.4 statistical software (SAS Institute, Cary, NC, USA) and all p-values presented are two-tailed. Although this is a feasibility trial we estimated an average number of 4 MRPs per patient at baseline and expected a reduction of 0.6% MRP (i.e 15%) per patient with a standard deviation of 1.5 MRPs, a power of 95%, an $\alpha=5\%$, and a dropout rate of 5%, resulting in a sample size of 100 participants in each group. Results are presented using the Consort Statement checklist for reporting of clinical trials (23).

**Results**

A total of 200 participants were recruited (100 to the intervention group and 100 in the control/standard of care group). Patients (155/77%) were recruited from the Sussex HIV Network of Hospitals (Brighton, Worthing, Chichester, Crawley). The largest centre is Brighton (cohort size 2,500 PLWH). Of the 100 participants allocated to the intervention group 87 received the MOR at baseline; baseline data were collected for all 100 participants receiving standard care. At 6 months a further 17 patients had withdrawn from the intervention group; six participants from the control group were lost to study follow-up. The main reasons for study discontinuation were patients unable or unwilling to attend a MOR consultation (13 at baseline and additional 17 at 6 months) and lost to follow up (6 control arm participants at 6
months). A total of 70 participants received their 6-month MOR, with data recorded for 94 standard care participants (Figure 2). No significant differences in baseline characteristics or clinical parameters between study groups were observed (Table 1).

**Medication-related problems**
A total of 93 MRPs were identified in the intervention group at baseline compared to only 2 in the standard of care group. The median (interquartile range [IQR]) number of MRP at baseline for the intervention group was 1 (0-6) and 0 (1-2) for the standard of care group. This difference was significant (p=0.001; z=-8.6; r: 0.6). At 6 months a further 33 new MRPs were identified in the intervention group vs 3 in the control group (p=0.001; z=-5.7; r =0.4). There was a significant reduction in the number of new MRPs at 6 months in the intervention group compared to baseline (p=0.001; Z=-3.7; r:0.2) (Figure 3). The most common MRPs identified at both time points in the intervention arm were DDIs, followed by need for dose adjustment (including where due to a DDI), and potential adverse drug reactions (Table 2).

**Non-ART medications:**
Overall, the median (range) of non-ART medications for both groups was 5 (0 to 17). A significantly greater number of non-ART drugs was recorded in the intervention group (mean [SD] 7.1 [3.6]) compared to the standard care group (mean [SD]= 4.5 (24)) (p<0.001; CI: 1.3 to 3.9), as only those non-ART drugs already documented in the electronic patient record were recorded for the control group, unless patients volunteered new information to the pharmacist when presenting their prescription for clinical review prior to dispensing. Although there was a reduction in the number of non-ART medications at 6 months (61 to 45) in the intervention group, the difference was not significant (p=0.217). Figure 4 shows the type of non-ART drugs for both study groups. The main differences between study groups in the type of non-ART drugs documented were among supplements and other less frequently used medications such as testosterone, and thyroid replacement therapy.

**Pharmacists’ recommendations**
MRPs in both study groups generated pharmacist recommendations: patient to resolve, GP to resolve, or HIV/ID physician to resolve. It is not possible to describe in detail all the recommendations given but they included: those for patients to resolve, such as stopping a
The MOR Study

supplement; for the GP to resolve, such as adjusting the dose of a non-ART medication; or for
the HIV physician to resolve, such as changing cART regimen when there was no safe
alternative to a currently-contraindicated non-ART medicine. Pharmacists fully resolved 42
(44%) of all MRPs identified in both study groups at baseline (n=95) and further 67 (51%) out
of the total of MRP including those unresolved from baseline (n=52) and newly identified at
6 months (n=36). A total of 22 out of 131 MRP remained unresolved at 6 months.

Intervention costs and impact of quality of life

On average, pharmacists spent 69 minutes on the baseline assessment and 67 minutes on the
follow-up assessment. The average cost of the review was £77 (estimated range £36-£211).
Given that not all patients incurred the full review cost included in all activities described
previously, the average cost of a MOR intervention visit including visit per patient was £43.
Median EQ-VAS score for all participants was 75 (1-100). No significant changes in health-
related quality of life EQ-VAS scores between MOR and standard care groups were observed
at baseline (p=0.860; CI:-2.8 to 10.4) or 6 months (p=0.896; CI: -8.3 to 7.1). Similarly, no
changes in EQ-VAS scores were observed at 6 months in any of the study groups compared
to baseline (MOR: p= 0.646; CI: -3.6 -5.7; standard of care: p= 0.12; CI:-5.5 to 0.66)

Patient and healthcare professional satisfaction:

Patient satisfaction questionnaires were completed by 38 patients (54%) who attended a
MOR. All respondents rated the service provided as excellent or very good. Most respondents
strongly agreed that after the MOR consultations they felt more confident managing their
medicines. Health care professional questionnaires were completed by 9 out of 31 (29%)
professionals involved with HIV care (6 doctors and 3 nurses). All respondents found the
information provided by the MOR very or somewhat useful and were very satisfied with the
service provided.

Discussion

This study provides evidence that the use of targeted MOR consultations within HIV
outpatient services is feasible and increases the identification of MRPs by specialist
pharmacists. The study found a significantly higher number of MRPs were detected using a
MOR at both baseline and 6 months, suggesting the importance of regular MORs for PLWH aged 50 years and older. Although the study inclusion criteria included younger PLWH with >1 comorbidity, most participants were aged at least 50, and there were no significant differences in baseline characteristics between the intervention and control arms. However, not all participants had a comorbidity or were taking any comedications, so the impact of MRPs may be even greater if targeted at those who would benefit most.

No effect on health-related quality of life (HRQoL) was demonstrated, which is consistent with systematic reviews of other SMR interventions (25). This may reflect a relatively minimal impact the majority of MRPs had on the experiential perception of participants’ quality of life, despite the potential for an MRP to cause significant harm. For example, resolving a DDI that reduces statin efficacy confers potential long-term benefit which is unlikely to manifest in any immediate improvement in quality of life. Similarly, if MRPs that reduce antiretroviral exposure are prevented or resolved before cART failure occurs, this is not expected to impact on quality of life. It is also possible that the EQ-5D-5L lacks specificity for the issues facing this particular study population. While the EQ-5D-5L has been validated for use in HIV populations (26), a ceiling effect has been reported, which may reduce its sensitivity in people who report good baseline HRQoL (27), also the specific impacts of polypharmacy and comorbidities in an older HIV population may not be reflected adequately in this broad measurement tool.

The higher number of dropouts in the intervention arm (13 before receiving baseline MOR and a further 17 who did not have a MOR at 6 months) likely reflects the additional pharmacist consultations compared with the control arm (standard care), as this could not always be combined with another scheduled clinic attendance (e.g. for a routine blood or medical appointment) due to the capacity constraints of the HIV pharmacy team. Similarly, some participants who had attended a baseline MOR at which no MRPs were identified may not have been motivated to prioritise the 6-month appointment if their medicines were unchanged and they had no new self-perceived MRPs. Contacting participants who cancelled or did not attend to reschedule appointments was an additional administrative burden for the pharmacy team.
This study has several limitations; firstly, it is a feasibility study and therefore was not powered to assess the intervention’s effectiveness. We calculated a sample size based on an a priori estimation on the number of MRPs identified and the reduction of MRPs over time, but we were unable to achieve our target number for the intervention group, therefore results must be interpreted with caution. Despite this, the clear difference between MRPs identified in those having medicines reviews suggest the intervention is effective. Secondly, as participants were recruited while attending clinic for a routine appointment (which in most cases occurs every 6 months), and pharmacist clinic appointments are not available at the same time as every medical or nurse clinic, many MOR consultations required an additional attendance. If this model was incorporated into standard care the additional time and expenditure would preclude some patients from having a MOR. However, since the SARS-CoV-2 pandemic different consultation modes have been introduced, including telephone and video consults, which would help overcome these barriers.

An important limitation of the current study is that the majority of participants were white men who have sex with men reflecting the demographics of the clinics’ cohorts. Consequently, generalisations to other groups cannot be made and further research is needed to examine the efficacy of MORs in different populations. The impact of factors such as economic deprivation on ability or willingness to attend were also not explored in this study. Our estimations of MOR costs were based on pharmacists’ time and did not take into account costs associated with MRPs such as unscheduled consultations, A&E visits and hospitalisations. Cost savings due to reducing unnecessary prescribing is another important economic outcome which was not assessed here. The quantifying of these costs was beyond the remit of this study, since this would require a fully powered sample size. Patients’ waiting time for consultations in relation to MRPs and associated opportunity costs should also be considered in future economic evaluations.

**Conclusion:**

This study demonstrated it was feasible for HIV pharmacists to conduct structured medication reviews using the MOR Toolkit in an HIV outpatient clinic, and that the intervention increased the number of medicine-related problems which were identified and resolved. MOR consultations were rated highly by patients and provided useful information to other healthcare professionals involved in their care. An increase in HIV pharmacist capacity would
be required to integrate MORs into standard care in some, if not all, HIV clinical services. Future work should explore and compare alternative delivery models and care pathways which utilise the skills of HIV pharmacists in secondary care and clinical pharmacists in primary care.

Disclosures
JV has received travel and research grants from and has been speaker/advisor for Merck, Janssen Cilag, Piramal Imaging, ViiV Healthcare and Gilead sciences. HLD has received honoraria and financial support for conference attendance from ViiV Healthcare and Gilead Sciences.

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12. NICE. NICE guideline: Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes, 2015. 


17. Sealed Envelope .


Figure 1. MOR Study flow chart

Inclusion criteria
- >50 years old on cART
- <50 years on cART requiring at least 1 non-ART medication

Figure 2. Participant flow chart

Assessed for eligibility (n=200)
- Excluded (n=0)

Randomized (n=200)
- Allocated to MOR (n=100)
  - Received MOR (n=87)
- Standard of care (n=100)
  - Received standard of care (n=100)

Discontinued intervention (n=17)
- Follow-Up (6 months)
- Lost to follow-up (n=6)

Analysed (n=70)
- Analysis (6 months)
- Analysed (n=94)

[Legend: MOR: medicines optimisation review]
Table 1. Baseline characteristics of patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MOR n= 87</th>
<th>Standard of care n=100</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Age, years*</td>
<td>59.5 (50-78)</td>
<td>60 (50-82)</td>
<td>NS</td>
</tr>
<tr>
<td>Male, n(%)</td>
<td>76 (87)</td>
<td>90 (90)</td>
<td>NS</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>White</td>
<td>78 (89)</td>
<td>92 (92)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>8 (9)</td>
<td>8 (8)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Sexuality, n(%)</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>MSM</td>
<td>66 (75)</td>
<td>86 (86)</td>
<td></td>
</tr>
<tr>
<td>Heterosexual</td>
<td>21 (25)</td>
<td>14 (14)</td>
<td></td>
</tr>
<tr>
<td>Years since HIV diagnosis*</td>
<td>17 (1-35)</td>
<td>18 (1-34)</td>
<td>NS</td>
</tr>
<tr>
<td>Years on ART*</td>
<td>13 (1-29)</td>
<td>13 (1-28)</td>
<td>NS</td>
</tr>
<tr>
<td>HIV based cART, n(%)</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>PI based</td>
<td>27 (31)</td>
<td>30 (30)</td>
<td></td>
</tr>
<tr>
<td>INSTI based</td>
<td>29 (33)</td>
<td>29 (29)</td>
<td></td>
</tr>
<tr>
<td>NNRTI based</td>
<td>31 (35)</td>
<td>41 (41)</td>
<td></td>
</tr>
<tr>
<td>CD4 Cell/ mL*</td>
<td>655 (98-1406)</td>
<td>557 (68-1609)</td>
<td>NS</td>
</tr>
<tr>
<td>VL &lt;40 copies/mL</td>
<td>95%</td>
<td>97.7%</td>
<td></td>
</tr>
</tbody>
</table>

* Median (interquartile range)

Figure 3. Number of new medication-related problems: MOR and standard care

[Legend: a. Total number of medication related problems for MOR vs standard of care at day 0 and 6 months. b. Reduction in total number of medication related problems in the MOR group at 6 months. *** p>0.001 results from Mann Whitney Rank test and ** Wilcoxon rank tests]; Y axis represent Mann Whitney or Wilcoxon rank mean scores
Figure 4. Type of non-ART medications
Table 2. Medication-related problem (MRP) type at 0 and 6 months: MOR and standard care

<table>
<thead>
<tr>
<th>MRP type</th>
<th>Day 0</th>
<th>6 months (new MRPs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MOR n=93</td>
<td>Standard of care n=2</td>
</tr>
<tr>
<td>Potential drug-drug interaction</td>
<td>34</td>
<td>1</td>
</tr>
<tr>
<td>Potentials adverse drug reaction</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Dose adjustment</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Problem with handling or</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>administration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unnecessarily complex regimen</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Inappropriate off label use</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Undertreatment</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*** p<0.001 results from Mann Whitney Rank test and ** Wilcoxon rank tests