Resistance-informed versus empirical management of viraemia in children and adolescents with HIV in Lesotho and Tanzania (GIVE MOVE trial): a multisite, open-label randomised controlled trial

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Summary

Background Children and adolescents with HIV taking antiretroviral therapy (ART) have high rates of viraemia. We assessed if genotypic resistance testing (GRT) to inform onward treatment improved treatment outcomes in Lesotho and Tanzania, two countries with little access to GRT.

Methods The Genotype-Informed Versus Empirical Management of Viremia (GIVE MOVE) open-label, parallel-group randomised controlled trial enrolled children and adolescents with HIV between the ages of 6 months and 19 years, taking ART, and with a viral load at least 400 copies per mL. Participants were recruited from ten clinical centres and hospitals in Lesotho and Tanzania. Participants were electronically randomly allocated 1:1 to receive either GRT with expert recommendation (GRT group) or repeat viral-load testing and empirical onward treatment (usual care group). Participants and study staff were not masked, but the endpoint committee and laboratory staff conducting viral-load testing were. Participants in both groups received at least three sessions of enhanced adherence counselling, and in the GRT group, blood for GRT assessed via Sanger sequencing was drawn at enrolment. The composite primary endpoint was death, hospitalisation, a new WHO HIV clinical stage 4 event, or not having documented viral suppression of less than 50 copies per mL at 36 weeks in the modified intention-to-treat population, which excluded participants who were retrospectively found to be ineligible after randomisation. Serious adverse events were analysed in the modified intention-to-treat population. The trial was registered with ClinicalTrials.gov (NCT04233242) and the trial status is completed.

Findings Between March 3, 2020, and July 5, 2022, 286 participants were enrolled and 284 were included in the modified intention-to-treat analysis (144 in the GRT group and 140 in the usual care group). Of these participants, 158 (56%) were female and 126 (44%) were male. Five (3%) in the GRT group and four (3%) in the usual care group did not complete follow-up but were included in the primary analysis. The median age across both groups was 14 years (IQR 9–16). The composite primary endpoint occurred in 67 (47%) participants in the GRT group and 73 (52%) in the usual care group (adjusted odds ratio 0·79 [95% CI 0·49 to 1·27]; adjusted risk difference –0·06 [95% CI –0·17 to 0·06]; p=0·34); all participants reaching the composite primary endpoint had no documented viral suppression at 36 weeks. No deaths were recorded, and only one clinical stage 4 event requiring hospitalisation occurred (in the usual care group); this was the only serious adverse event recorded in the study.

Interpretation GRT-informed management did not significantly improve treatment outcomes for children and adolescents with viraemia while taking ART.

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For the Sesotho translation of the abstract see **Online** for appendix 1

For the Swahili translation of the abstract see **Online** for appendix 2

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Introduction

Globally, 2·6 million children and adolescents are living with HIV.[1] Treatment failure is a common concern, with far fewer children and adolescents reaching viral suppression with antiretroviral therapy (ART) compared with adults.[2]

Management of viraemia in people taking ART necessitates differentiation between underlying causes, notably viral drug resistance and suboptimal adherence, requiring distinct interventions. Although widely used in high-income countries, genotypic resistance testing (GRT) to inform clinical management is operationally complex, cost and labour intensive, and rarely available in under-resourced health systems. Despite several calls for increased access to GRT for population-based surveillance and potentially individualised clinical management,[3–5] evidence on the effectiveness[6,7] and cost-effectiveness[8–10] of GRT-informed management of

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See Online for appendix 3

Research in context

Evidence before this study

WHO lists the role of drug resistance testing among children and adolescents, as well as people taking dolutegravir-based antiretroviral therapy (ART), as a key research gap. Several randomised controlled trials published well over a decade ago assessed the effect of resistance testing compared with usual care without resistance testing, mostly including ART regimens that are no longer in use. A systematic review including publications up to January, 2018, identified 11 trials published between 1999 and 2006, all conducted in Europe, the USA, or Brazil, and only two included children. These two trials, enrolling 170 and 49 children, reported no difference in virological outcomes. Overall, the systematic review concluded that resistance testing probably improved virological outcomes in people with failing ART. We searched PubMed on March 18, 2024, with the search strategy shown in appendix 3 (p 2), for trials published between January, 2018, and March, 2024. There were no specific inclusion or exclusion criteria. The REVAMP trial, conducted in South Africa and Uganda, directly compared management of viraemia with and without resistance testing in adults with viraemia of at least 1000 copies per mL while taking non-nucleoside reverse transcriptase inhibitor-based ART. This trial found no difference in viral suppression at 9 months between the study groups. The Opt4Kids trial, conducted among children in Kenya, compared an intervention package including more frequent point-of-care viral-load testing with targeted resistance testing upon detection of viraemia with usual care. This trial included children regardless of their viral load and showed no difference in viral suppression at 12 months. Although early trials recruiting mostly in Europe and the USA showed a potential benefit of resistance-informed onward treatment for reaching viral suppression, the more recent Opt4Kids (albeit implementing genotypic resistance testing as part of a broader intervention package and also including children with viral suppression at enrolment) and REVAMP trials did not show such an effect. Thus far, no trial has assessed the effect of resistance-informed clinical management on viral suppression in the era of dolutegravir.

Added value of this study

GIVE MOVE is the largest trial to assess the effect of GRT-informed management of viraemia in children and adolescents, and the first in any age group to do so in the context of dolutegravir-based ART. We observed no difference in treatment outcomes among children and adolescents with viraemia of at least 400 copies per mL receiving onward treatment informed by resistance testing and an expert committee recommendation versus usual care. Results were consistent across prespecified sensitivity analyses and for secondary endpoints.

Implications of all the available evidence

Our findings suggest that broad implementation of resistance testing does not significantly improve treatment outcomes for children and adolescents with HIV viraemia. A high proportion of children and adolescents without treatment-relevant mutations detected at baseline had ongoing viraemia at 36 weeks, suggesting suboptimal adherence to be the primary driver of viraemia in this population. Further research is needed to better identify individuals or subgroups with an elevated risk of resistance and who are most likely to benefit from rapid access to resistance testing. In conclusion, together with previous evidence, GIVE MOVE does not support prioritising broad implementation of resistance testing for all people with an unsuppressed HIV viral load.

viraemia is mixed and mostly pertains to adults, high-income countries, or people taking now-obsolete ART regimens. Current WHO guidelines do not recommend GRT for routine use; instead, routine care includes adherence counselling and repeat viral-load testing with empirical selection of onward ART. However, WHO guidelines list the role of resistance testing among children and adolescents as well as people taking ART containing the integrase strand-transfer inhibitor (INSTI) dolutegravir as key research gaps.[11]

We conducted a randomised trial assessing whether GRT and expert recommendations to inform management of viraemia improve clinical and virological treatment outcomes versus usual care among children and adolescents with HIV.[12]

Methods

Study design

The Genotype-Informed Versus Empirical Management of Viremia (GIVE MOVE) open-label, parallel-group randomised controlled trial assessed 36-week outcomes among children and adolescents with viraemia while taking ART. The intervention group received GRT and GRT-informed expert recommendation for onward treatment, whereas the control group received usual care. Aligned with WHO and national guidelines, usual care consisted of several sessions of enhanced adherence counselling (ie, structured adherence counselling provided upon detection of viraemia), a confirmatory viral-load test, and onward treatment informed by the confirmatory viral-load and clinical assessment.[11,13–15]

GIVE MOVE was conducted at ten clinical centres and hospitals in Lesotho and Tanzania (appendix 3 p 3). The trial was approved in Lesotho by the National Health Research Ethics Committee (first approval identifier 229-2019), and in Tanzania by the National Institute for Medical Research (NIMR/HQ/R.8a/Vol IX/3442), the Tanzania Medicines and Medical Devices Authority (TMDA0020/CTR/0003/03), and the Ifakara Health Institute Institutional Review Board (12-2020). Additionally, the Ethikkommission Nordwest und Zentralschweiz in Switzerland provided a statement (Req-2019-01275)

confirming the trial meets all ethical requirements for a Swiss research project. A study protocol manuscript has been published previously.[12] The trial was registered with ClinicalTrials.gov (NCT04233242), where a full protocol and statistical analysis plan are available.

Participants

Children and adolescents aged between 6 months and 19 years who were receiving care at a study site, had been on the same ART regimen for at least 6 months, had a routine HIV viral load of at least 400 copies per mL taken less than 16 weeks before screening, and with written informed consent (as described previously[12]) were eligible. The main exclusion criteria were having acute illness requiring hospitalisation, having an indication for treatment switch, being pregnant, or breastfeeding at the time of screening; having initiated enhanced adherence counselling more than 2 weeks before screening; and having received a resistance test in the previous 12 months. During the study, the protocol was amended for two eligibility criteria: the initial inclusion criterion of being on a first-line ART regimen at enrolment was dropped as the roll-out of newer ART regimens has blurred the distinction between first-line and second-line ART, and the acceptable time between phlebotomy for the last (elevated) viral load and screening was increased from 12 weeks to 16 weeks because clients often only return for their next clinic visit approximately 3 months after a routine viral-load test and otherwise eligible participants were thus being missed. Data on sex were retrieved from medical records.

Randomisation and masking

Participants were randomly assigned via concealed 1:1 allocation to either the GRT or usual care groups with the electronic data capture software MACRO version 4.8.1 (Ennov, Paris, France). Randomisation used permuted blocks with varying block size and was stratified by country (ie, Lesotho or Tanzania), age (ie, <12 years or ≥12 years), and ART core agent class at enrolment (non-nucleoside reverse transcriptase inhibitor [NNRTI], protease inhibitor, or INSTI). The randomisation sequence was generated by a statistician not involved in the study. Enrolment, trial group allocation, and subsequent study procedures were completed by trained routine staff at each site. Participants and study staff were not masked due to the nature of the intervention. The endpoint committee and laboratory staff conducting viral-load testing were masked.

Procedures

Participants were followed up for 36 weeks (window 32–44 weeks) or until 24 weeks (20–28 weeks) after the decision visit for onward care, whichever occurred later. The decision visit for onward care was defined as the first visit following the availability of a GRT-informed expert committee recommendation (GRT group) or a confirmatory viral-load result (usual care group). Participants had protocol-defined visits at enrolment (baseline visit) and at 4 weeks (window 3–5 weeks), 8 weeks (6–10 weeks; usual care group only), 12 weeks (10–14 weeks), 24 weeks (20–28 weeks), and 36 weeks (32–44 weeks). The 24-week post-decision visit typically overlapped with another study visit (appendix 3 p 10). Participants in both groups received at least three sessions of enhanced adherence counselling, namely at enrolment and the subsequent two clinic visits. Enhanced adherence counselling is included in national guidelines in Lesotho and Tanzania and was provided in line with routine care.[11,14,15] Enhanced adherence counselling is generally provided by a nurse, counsellor, or other health-care facility team member and typically involves an assessment of adherence and potential adherence barriers—including knowledge, psychological, emotional, and socioeconomic factors—and codeveloping an individualised adherence plan. Family members or other treatment supporters can be involved in the process, depending on individual context.[14,15]

In the GRT group, blood for GRT was drawn at enrolment (ie, baseline visit) or as soon as possible thereafter. GRT consisted of Sanger sequencing as per the respective laboratories' routine protocols. GRT was attempted for the protease and reverse transcriptase regions of *pol*, and, in individuals taking INSTI-based ART, for the integrase region of *pol* as well. Results were shared with a GRT expert committee consisting of one virologist and five clinicians from Switzerland, Lesotho, and Tanzania (members listed in the Acknowledgments). At least two committee members provided a recommendation for onward care for each participant in the GRT group. GRT results, committee members' recommendations, and a consolidated recommendation were returned to the respective site team, who had the right to overrule any recommendation. Onward care (ie, the decision to maintain unchanged ART or to adapt the regimen) was thus informed by GRT, the GRT expert committee recommendation, and the health-care provider's adherence assessment and decision in the GRT group. The usual care group followed the WHO guidelines[11,13] with confirmatory viral-load testing at 8 weeks. Onward care was informed by the confirmatory viral-load result, adherence assessments, and the health-care provider decision in the usual care group. Only serious adverse events were systematically captured (appendix 3 p 11). Serious adverse events were defined as any untoward medical occurrence that results in death or is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or substantial disability or incapacity, or causes a congenital anomaly or birth defect. Serious adverse events were assessed by the sponsor investigator for their potential relationship with the study intervention and for seriousness by use of the Division of AIDS' *Table for Grading the Severity of Adult and Pediatric Adverse Events* (version 2.1).[16]

Outcomes

The composite primary endpoint was the occurrence of any of the following during the follow-up period (36 weeks): (1) death due to any cause; (2) hospital admission lasting at least 24 h and possibly, probably, or definitely related to HIV or ART; (3) a new WHO stage 4 event (excluding lymph node tuberculosis, stunting, oral or genital herpes simplex infection, and oesophageal candidiasis); or (4) not having a documented viral load of less than 50 copies per mL at 36 weeks' (window 32–44 weeks) follow-up. For hospitalisations and new WHO clinical stage 4 events, an independent endpoint committee (members listed in the Acknowledgments) masked to the study group assessed whether the respective endpoint was met. The component of not having a documented viral load of less than 50 copies per mL could be reached either through not having a within-window viral-load measurement or having a within-window measurement of at least 50 copies per mL. The threshold of 50 copies per mL aligns with the WHO definition of an undetectable viral load.[11] The rationale for the composite endpoint was to be able to provide GRT even in the control group in case of hospitalisation or a new WHO clinical stage 4 event without compromising the analysis.

Secondary endpoints were: (1) each individual component of the primary endpoint; (2) loss to follow-up, defined as not having a documented clinic visit at 36 weeks; (3) a viral load of at least 50 copies per mL at 36 weeks among participants with a viral-load result at this timepoint; and (4) the composite endpoint used for the primary endpoint assessed at 24 weeks (window 20–28 weeks) after the decision visit. The 36-week timeframe in the primary and several secondary endpoints was selected to allow at least 24 weeks to achieve suppression between the decision visit and endpoint assessment, assuming the decision visit was not delayed beyond 12 weeks (appendix 3 p 10). The composite secondary endpoint at 24 weeks after the decision visit accounted for different times to the decision visit, either between groups or because of operational delays.

Resistance-associated mutations were defined and classified in line with the Stanford HIVdb algorithm[17] and are shown as reported to the GRT expert committee and site clinicians. Treatment-relevant resistance was defined as at least potential low-level resistance to any drug in the current ART regimen.

In a post-hoc analysis, we descriptively report the data informing onward care, implemented onward care, and the proportion reaching the primary endpoint stratified by these two factors. For the GRT group, we show GRT outcome categories (ie, successful; no GRT, viral load <50 copies per mL; no GRT, viral load 50–399 copies per mL; and no GRT, viral load >399 copies per mL), the GRT expert committee recommendation for onward care (ie, no change, consider change, change for convenience or tolerability, and change due to resistance), implemented changes to ART (ie, not changed, backbone changed, core agent changed, and core agent and backbone changed), and the stratified proportion who had a primary endpoint event. Consolidated GRT expert committee recommendations were first classified separately for the ART core agent and the nucleoside reverse transcriptase inhibitor backbone. If either recommendation was classified as change due to resistance, this classification was used for the overall recommendation. If one recommendation was change for convenience or tolerability and the other was consider change, the overall recommendation was classified as change for convenience or tolerability. For the usual care group, we show the result of the confirmatory viral load (ie, <50 copies per mL, 50–399 copies per mL, and >399 copies per mL), the implemented changes to ART, and the stratified proportion reaching the primary endpoint.

Statistical analysis

On the basis of data from the sites, literature at the time of study design,[18–22] and potential benefits of GRT-informed care,[6] we hypothesised that 35% of participants in the usual care group and 20% in the GRT group would reach the primary endpoint. With a Pearson's χ^2 test, a sample size of at least 138 participants per group provides 80% power with a type I error rate of 5% to test this hypothesis.

Baseline characteristics are presented for the modified intention-to-treat (mITT) population, consisting of all randomly assigned participants other than those retrospectively found to be ineligible, and by randomised group, with medians and IQRs for continuous variables and numbers and percentages for categorical variables. The primary endpoint was analysed with logistic regression models adjusting for the stratification factors in the mITT population. Results are reported as adjusted odds ratios (aORs) with 95% CIs, and as adjusted absolute risk differences (aRDs) with 95% CIs estimated with the delta method. We repeated this analysis in the per-protocol population, which additionally excluded participants considered to have had a major protocol deviation. In sensitivity analyses, the primary endpoint analysis was repeated with alternative definitions of viral suppression (ie, <400 copies per mL to align with the threshold used for eligibility, and <1000 copies per mL to align with the WHO threshold for virological failure). We assessed effect modification of the primary endpoint by any of the randomisation stratification factors and sex by incorporating an interaction term between the trial group and the effect modifier. Effect estimation by subgroup was foreseen if the interaction term was found to be significant. For secondary endpoints, logistic regression models estimated aORs and aRDs as for the primary outcome except when there were few events, in which case only proportions were presented.

As post-hoc analyses, we descriptively report the primary endpoint stratified by treatment-relevant resistance in the GRT group, and by the confirmatory viral-load result in the usual care group. We created Sankey diagrams displaying data informing onward treatment, implemented adjustments to ART, and the proportion reaching the primary endpoint.

An interim analysis was planned once 50% of the intended sample size had completed the 36-week follow-up or reached the primary endpoint. Preplanned stopping rules allowed early termination for success if a significant difference for the composite primary endpoint was achieved with the conservative Haybittle-Peto stopping boundary of p=0·001. Early stopping for inefficacy was planned if the aOR was greater than 1 and the two-sided 95% CI did not contain the hypothesis (ie, aOR 0·57). The preplanned interim analysis was conducted by an external statistician on May 12, 2022. The data safety monitoring board recommended continuation of the trial. Analyses were done with Stata version 16. Sankey diagrams were created using the networkD3 package in R version 4.3.1.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between March 3, 2020, and July 5, 2022, 545 individuals were screened and 286 were enrolled and randomly assigned. Two participants (one per group) were ineligible at enrolment but were mistakenly enrolled and randomised; they were subsequently excluded from the mITT population, resulting in 284 participants who fulfilled inclusion criteria and were randomly assigned to groups. 144 (51%) were assigned to the GRT group and 140 (49%) to the usual care group (figure 1). Five (3%) participants in the GRT group and four (3%) in the usual care group were lost to follow-up, but included in the mITT analyses. There were 17 participants excluded from per-protocol analyses in the usual care group and 31 excluded from the GRT group. Baseline characteristics were balanced between the study groups (table 1; appendix 3 pp 4–5).

The composite primary endpoint indicating adverse treatment outcomes occurred in 67 (47%) of 144 participants in the GRT group and 73 (52%) of 140 in

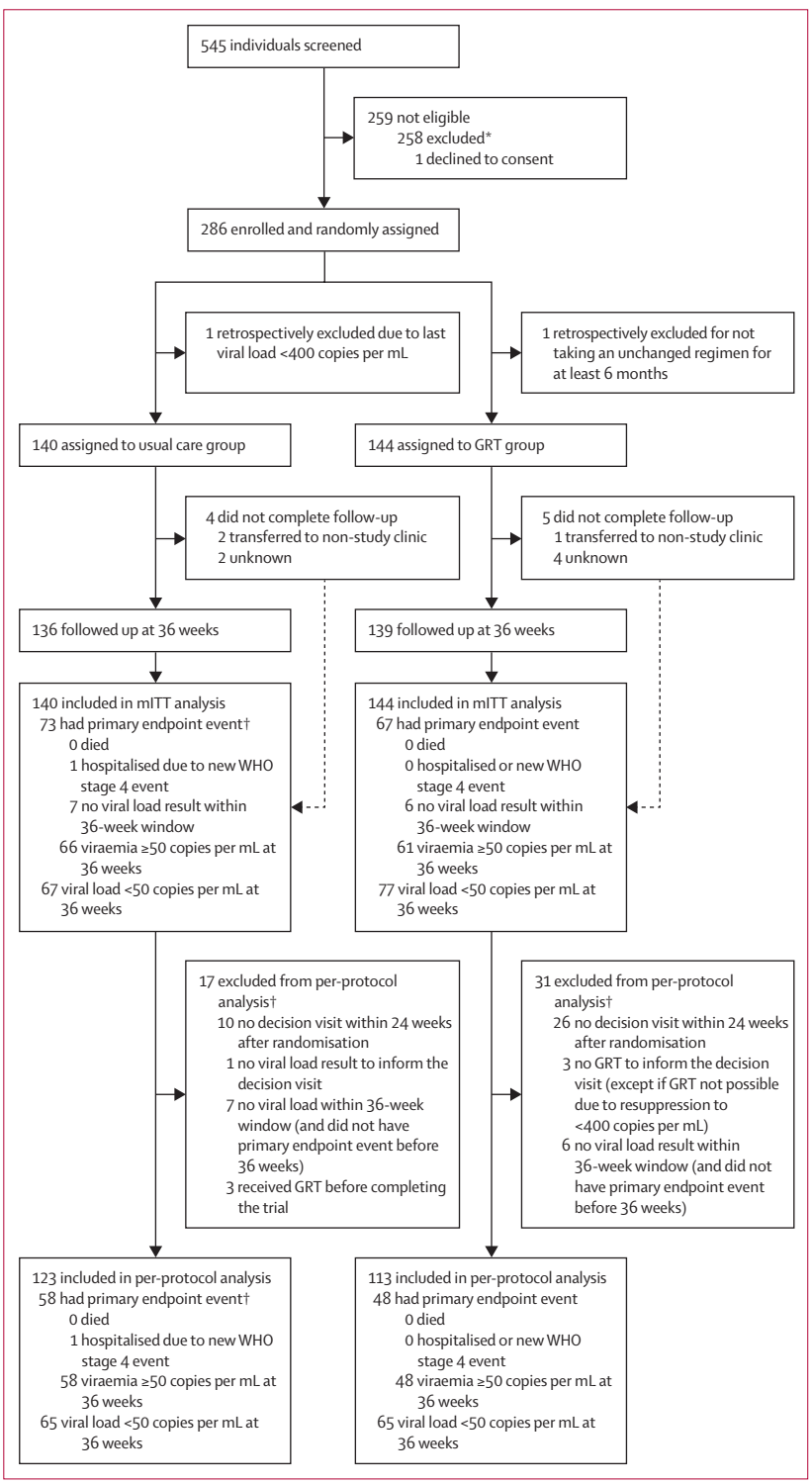

Figure 1: **Trial profile**

GRT=genotypic resistance testing. mITT=modified intention-to-treat. *Thereof (multiple reasons might apply to the same individual): 79 were not on first-line antiretroviral therapy (criterion later dropped), 65 had a phlebotomy too long before screening, 42 initiated enhanced adherence counselling more than 2 weeks before screening, 33 were not within age range, 28 had a last viral load of less than 400 copies per mL, 17 had not been on unchanged antiretroviral therapy for at least 6 months, 12 (participants or caregivers) could not be contacted, six had an indication for treatment switch, two had acute illness requiring hospitalisation, two were not in care in a study site, two had an intention to transfer to a non-study clinic, one had their antiretroviral therapy stopped, one had a resistance test in the previous 12 months, and three had no data. †Multiple reasons might apply to the same individual.

	Usual care group (n=140)	GRT group (n=144)	Total (N=284)
Demographic and clinical factors at enrolment			
Country			
Lesotho	99 (71%)	104 (72%)	203 (71%)
Tanzania	41 (29%)	40 (28%)	81 (29%)
Sex			
Female	83 (59%)	75 (52%)	158 (56%)
Male	57 (41%)	69 (48%)	126 (44%)
Age	14 (9–16)	13 (9–16)	14 (9–16)
≥6 months to <12 years	58 (41%)	58 (40%)	116 (41%)
≥12 years to 19 years	82 (59%)	86 (60%)	168 (59%)
Viral load before enrolment, copies per mL	6925 (1463–28 800)	5730 (1465–43 500)	6600 (1463–36 850)
400–999	25 (18%)	23 (16%)	48 (17%)
1000–99 999	101 (72%)	101 (70%)	202 (71%)
≥100 000	14 (10%)	20 (14%)	34 (12%)
WHO clinical stage			
1	136 (97%)	138 (96%)	274 (96%)
2	1 (1%)	4 (3%)	5 (2%)
3	3 (2%)	0	3 (1%)
4	0	2 (1%)	2 (1%)
CD4 cell count, cells per μL			
For participants aged <5 years (n=38)	1187 (892–1651)	837 (711–1318)	1057 (729–1480)
Missing	4	6	10
For participants aged ≥5 to <19 years (n=246)	557 (398–783)	580 (417–818)	575 (403–814)
Missing	16	19	35
Immunosuppression*			
Not substantial	67 (56%)	75 (63%)	142 (59%)
Mild	31 (26%)	19 (16%)	50 (21%)
Advanced	14 (12%)	14 (12%)	28 (12%)
Severe	8 (7%)	11 (9%)	19 (8%)
Missing	20	25	45
Weight, kg	36 (23–45)	32 (21–44)	34 (22–45)

(Table 1 continues in next column)

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	Usual care group (n=140)	GRT group (n=144)	Total (N=284)
Treatment at enrolment			
Time since initiation of first documented ART regimen, years	7 (4–10)	6 (3–10)	6 (3–10)
Time since initiation of current ART regimen, years	2 (1–3)	2 (1–3)	2 (1–3)
ART regimen at enrolment			
NNRTI	6 (4%)	7 (5%)	13 (5%)
Protease inhibitor	50 (36%)	51 (35%)	101 (36%)
INSTI	84 (60%)	86 (60%)	170 (60%)
Missed ≥1 dose of ART over the past 4 weeks (self-reported)			
Yes	41 (30%)	54 (38%)	95 (34%)
No	81 (59%)	71 (50%)	152 (54%)
Unknown	16 (12%)	17 (12%)	33 (12%)
Missing	2	2	4
No drug intake for 2 days or more over the past 4 weeks (self-reported)			
Yes	30 (22%)	43 (30%)	73 (26%)
No	91 (66%)	80 (56%)	171 (61%)
Unknown	17 (12%)	19 (13%)	36 (13%)
Missing	2	2	4
Socioeconomic factors			
At least one parent known to be deceased	61 (44%)	68 (47%)	129 (45%)
Known full orphan	15 (11%)	21 (15%)	36 (13%)
Travel time to health-care facility (one way), min	60 (30–120)	60 (30–90)	60 (30–120)
Cost of travel to health-care facility (one way), US$	1·29 (0·08–19·01)	1·22 (0·39–24·03)	1·26 (0·08–24·03)

Data are median (IQR) or n (%). ART=antiretroviral therapy. GRT=genotypic resistance testing. INSTI=integrase strand-transfer inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. *Defined on the basis of CD4 cell count or percentages with age-dependent ranges (appendix 3 p 6).

Table 1: **Participant characteristics at enrolment**

the usual care group, with no significant difference between groups (aOR 0·79 [95% CI 0·49 to 1·27]; aRD –0·06 [–0·17 to 0·06]; p=0·34; table 2).

In the per-protocol analysis, 48 (42%) of 113 participants in the GRT group and 58 (47%) of 123 in the usual care group had a primary endpoint event (aOR 0·84 [95% CI 0·50 to 1·42]; aRD –0·04 [–0·17 to 0·08]; p=0·51). In both groups, but more so in the GRT group, the main reason for exclusion from per-protocol analysis was having a delayed decision visit for onward care (figure 1). Increasing the threshold for viral suppression to less than 400 copies per mL or less than 1000 copies per mL in the mITT population did not meaningfully alter outcomes. Prespecified subgroup analyses were not conducted as the interaction terms were not significant (table 2).

Secondary endpoints did not differ significantly between study groups (table 2). One (1%) participant in the usual care group was hospitalised with miliary tuberculosis, fulfilling criteria for the two secondary endpoints of hospitalisation and having a new WHO clinical stage 4 event. This event was reported at the scheduled 36-week visit, when the participant also had ongoing viraemia, and was also the only recorded serious adverse event in the study. No further hospitalisations or WHO clinical stage 4 events and no deaths occurred during the study period. The proportion of participants without a documented viral load of less than 50 copies per mL at 36 weeks was 67 (47%) of 144 in the GRT group and 73 (52%) of 140 in the usual care group (aOR 0·79 [95% CI 0·49 to 1·27]; aRD –0·06 [–0·17 to 0·06]; p=0·34). Five (3%) participants in the GRT group and four (3%) in the usual care group were lost to follow-up. Among those with a viral-load result at 36 weeks, 61 (44%) of 138 in the GRT group and 66 (50%) of 133 in the usual care group

had viraemia of at least 50 copies per mL (aOR 0·82 [0·51 to 1·34]; aRD –0·05 [–0·16 to 0·07]; p=0·44).

In post-hoc analyses in the GRT group, GRT was successful for 84 (58%) individuals; among the remaining GRT group participants, the viral load had dropped to less than 400 copies per mL in 58 (40%) participants, and GRT failed despite a viral load of at least 400 copies per mL in two (1%) participants (table 3). Among participants with a GRT result, 52 (62%) of 84 harboured mutations conferring resistance to any drug class; 31 (37%) had less than three fully active drugs in their baseline regimen, 27 (32%) had less than two, and seven (8%) had none (table 3). The primary endpoint was reached by 19 (32%) of 60 participants without sequencing data, 33 (62%) of 53 with no treatment-relevant resistance at baseline, and 15 (48%) of 31 with treatment-relevant resistance at baseline (figure 2). The number of observed resistance-associated mutations are shown in appendix 3 (pp 7–8). Changes to ART were more common in the GRT group (49 [34%]) than the usual care group (19 [14%]; figure 2; appendix 3 p 9).

In post-hoc analyses in the usual care group, the primary endpoint was reached by 20 (32%) of 65 participants with a confirmatory viral load of less than 50 copies per mL, 15 (52%) of 29 with a confirmatory viral load of 50–399 copies per mL, and 35 (81%) of 43 with a confirmatory viral load of at least 400 copies per mL, and three (100%) of three participants who did not receive a confirmatory viral load test (figure 2).

Discussion

The GIVE MOVE trial assessed whether GRT-informed management improves treatment outcomes among children and adolescents with HIV viraemia while taking ART. We observed no significant difference in

	Usual care group	GRT group	Adjusted odds ratio (95% CI)	Adjusted risk difference (95% CI)	p value
Primary endpoint, mITT analysis	73/140 (52%)	67/144 (47%)	0·79 (0·49 to 1·27)	–0·06 (–0·17 to 0·06)	0·34
Primary endpoint, sensitivity analyses					
Per-protocol	58/123 (47%)	48/113 (42%)	0·84 (0·50 to 1·42)	–0·04 (–0·17 to 0·08)	0·51
mITT, viral suppression defined as <400 copies per mL	53/140 (38%)	48/144 (33%)	0·81 (0·50 to 1·33)	–0·05 (–0·16 to 0·06)	0·41
mITT, viral suppression defined as <1000 copies per mL	45/140 (32%)	40/144 (28%)	0·80 (0·48 to 1·34)	–0·04 (–0·15 to 0·06)	0·41
Primary endpoint, subgroup analyses (mITT)					
By sex	..	..	..	..	0·39*
Male	34/57 (60%)	33/69 (48%)	..	..	..
Female	39/83 (47%)	34/75 (45%)	..	..	..
By age	..	..	..	..	0·85*
≥6 months to <12 years	33/58 (57%)	29/58 (50%)	..	..	..
≥12 years to 19 years	40/82 (49%)	38/86 (44%)	..	..	..
By country	..	..	..	..	0·47*
Lesotho	53/99 (54%)	47/104 (45%)	..	..	..
Tanzania	20/41 (49%)	29/40 (50%)	..	..	..
By ART regimen at enrolment	..	..	..	..	..
NNRTI	4/6 (67%)	2/7 (29%)	..	..	..
Protease inhibitor	32/50 (64%)	30/51 (59%)	..	..	0·27*
INSTI	37/84 (44%)	35/86 (41%)	..	..	0·24*
Secondary endpoints (mITT)					
All-cause mortality	0/140	0/144	..	..	NE
Hospital admission of ≥24 h†	1/140 (1%)	0/144	..	..	NE
New WHO stage 4 event (with some exclusions)	1/140 (1%)	0/144	..	..	NE
No documentation of a viral load <50 copies per mL at 36 weeks	73/140 (52%)	67/144 (47%)	0·79 (0·49 to 1·27)	–0·06 (–0·17 to 0·06)	0·34
Loss to follow-up	4/140 (3%)‡	5/144 (3%)§	..	..	NE
Viral load ≥50 copies per mL among those with a viral load result at 36 weeks	66/133 (50%)	61/138 (44%)	0·82 (0·51 to 1·34)	–0·05 (–0·16 to 0·07)	0·44
Composite endpoint at 24 weeks after the decision visit	77/140 (55%)	83/144 (58%)	1·12 (0·70 to 1·80)	0·03 (–0·09 to 0·14)	0·64

ART=antiretroviral therapy. GRT=genotypic resistance testing. INSTI=integrase strand-transfer inhibitor. mITT=modified intention-to-treat. NE=not estimable. NNRTI=non-nucleoside reverse transcriptase inhibitor. *p value from the interaction term between the trial group and this variable. †Possibly, probably, or definitely related to HIV, ART, or both. ‡Includes two individuals recorded as transferred to a non-study clinic. §Includes one individual recorded as transferred to a non-study clinic.

Table 2: **Primary and secondary analyses and endpoints**

	GRT group (n=144)
GRT outcome	
No GRT, viral load <50 copies per mL	44 (31%)
No GRT, viral load 50–399 copies per mL	14 (10%)
No GRT, viral load ≥399 copies per mL	2 (1%)
GRT successful (at least protease and reverse transcriptase regions of *pol* gene)	84 (58%)
Integrase region of *pol* gene sequenced, in participants taking INSTI-based ART with successful GRT (n=38)	15/38 (39%)
Integrase region of *pol* gene not sequenced, in participants taking INSTI-based ART with successful GRT (n=38)*	23/38 (61%)
Days from baseline to phlebotomy for GRT	
Among participants with no GRT result (resuppression or no result, n=60)	0·0 (0–3·5)
Among participants with successful GRT (n=84)	0·0 (0–1·0)
Among participants with successful GRT (n=84)	
HIV subtype	
A	8/84 (10%)
C	74/84 (88%)
D	2/84 (2%)
At least one resistance mutation†	
No	32/84 (38%)
Yes	52/84 (62%)
At least one NRTI resistance mutation	
No	52/84 (62%)
Yes	32/84 (38%)
At least one NNRTI resistance mutation	
No	44/84 (52%)
Yes	40/84 (48%)
At least one protease inhibitor resistance mutation	
No	78/84 (93%)
Yes	6/84 (7%)
At least one INSTI resistance mutation	
No	14/84 (17%)
Yes‡	1/84 (1%)
No data, not taking INSTI-based ART	46/84 (55%)
No data, taking INSTI-based ART*	23/84 (27%)
Susceptibility to lamivudine or emtricitabine (taken by all in baseline regimen)	
Susceptible	54/84 (64%)
High-level resistance	30/84 (36%)
Susceptibility to second NRTI (other than lamivudine or emtricitabine) of baseline regimen	
Susceptible	58/84 (69%)
Low-level resistance	15/84 (18%)
Intermediate resistance	2/84 (2%)
High-level resistance	9/84 (11%)
Susceptibility to core agent of baseline regimen†	
Susceptible	75/84 (89%)
High-level resistance§	9/84 (11%)
Number of fully active drugs in baseline regimen†	
3	53/84 (63%)
2	4/84 (5%)
1	20/84 (24%)
0	7/84 (8%)

Data are median (IQR) or n (%). ART=antiretroviral therapy. GRT=genotypic resistance testing. INSTI=integrase strand-transfer inhibitor. NRTI=nucleoside reverse transcriptase inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. *Sequencing of the integrase region was completed post hoc for 17 of 23 individuals: 16 had no INSTI resistance-associated mutations and one had T97A conferring potential low-level resistance against first-generation INSTIs but not against dolutegravir. †No resistance to the integrase region of pol gene was assumed if the integrase region was not sequenced. ‡The detected resistance-associated mutations were L74M and Q95K, conferring potential low-level resistance against first-generation INSTIs but not against dolutegravir. §Thereof six individuals taking NNRTI-based ART and three taking protease inhibitor-based ART at enrolment.

Table 3: **Baseline GRT outcomes as reported to the GRT expert committee**

clinical and virological outcomes with GRT and expert recommendation compared with usual care. Treatment changes were more common in the GRT than in the usual care group, possibly because of the involvement of a GRT expert committee who also made recommendations for minor treatment modifications (especially single-drug substitutions) on the basis of convenience or tolerability. Even under trial conditions, over 40% of all participants still had viraemia at 36 weeks' follow-up, underlining the difficulty of reaching viral suppression in this population.

Previous randomised controlled trials[6,7] and cost-effectiveness modelling studies[8–10] on GRT-informed management of viraemia have had mixed results. A systematic review published in 2018 identified 11 trials on the effectiveness of genotypic or phenotypic resistance testing and concluded that resistance-informed care probably improves viral suppression.[6] However, the included trials were all published between 1999 and 2006, did not include modern-day ART regimens, and were mostly conducted among adults in high-income countries, such that implications for modern-day paediatric and adolescent care in low-income and middle-income countries are unclear. Of note, the included trials focusing on children did not observe a difference in virological outcomes.[6,23] The more recent REVAMP trial, conducted in South Africa and Uganda, enrolled adults with viraemia while taking NNRTI-based ART and found no difference in virological outcomes at 9 months with or without GRT, with 63% of participants with and 61% without GRT reaching viral suppression.[7] Finally, the Opt4Kids trial, testing intensified point-of-care monitoring of viral loads coupled with availability of GRT among children in Kenya, found no difference in outcomes between this intervention and standard care.[24]

At present, WHO does not recommend GRT except as an option when feasible for specific situations, such as guiding the choice of first-line ART if dolutegravir is unavailable or to optimise third-line ART.[11] These

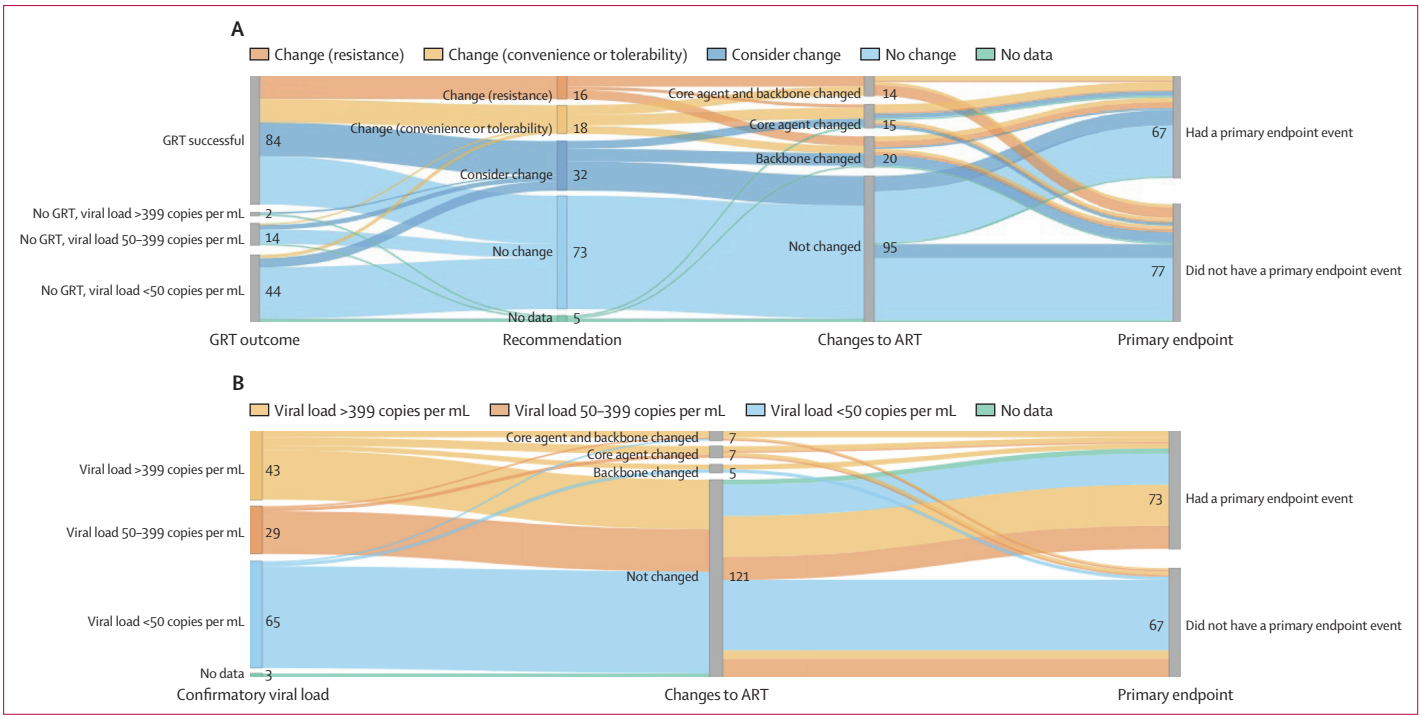

Figure 2: **Sankey diagram of available information informing onward decision, implemented changes to ART, and 36-week primary endpoint outcomes, by trial group**
(A) GRT outcomes, recommendations to inform onward care, and implemented changes in the GRT group. When a recommendation was available, all changes corresponded to (an option provided within) the recommendation. The colours of the flows indicate the GRT expert committee recommendation. (B) Outcomes of confirmatory viral-load testing to inform onward care and implemented changes in the usual care group. The colours of the flows indicate the confirmatory viral-load category. Numbers on both diagrams are numbers of participants within each category. The composite primary endpoint was death, hospitalisation, a new WHO HIV clinical stage 4 event, or not having documented viral suppression of less than 50 copies per mL at 36 weeks. ART=antiretroviral therapy. GRT=genotypic resistance testing.

guidelines highlight the role of GRT in the context of dolutegravir-based ART and for children and adolescents as a key research gap—a gap GIVE MOVE attempted to fill. Based on our findings and previous evidence,[7,23,24] timely provision of GRT without clinical triaging criteria is unlikely to be effective or cost-effective. Although resistance-associated mutations were not rare in GIVE MOVE, suboptimal adherence appeared to be the major driver of viraemia. Nevertheless, several individuals in the GRT group—notably three participants with high-level resistance to a protease inhibitor as their core agent—would have been unlikely to receive therapeutically indicated changes to ART without GRT. Together with reports of emerging resistance against dolutegravir-based ART,[25–28] this finding suggests that more targeted criteria are needed to predict the individual risk of resistance and guide the cost-effective use of GRT. Point-of-care therapeutic drug monitoring could help to limit GRT to individuals with HIV who have detectable concentrations of antiretroviral drugs in their blood and to instead provide immediate adherence support to individuals with no recent ART intake.[29]

The need for better interventions, including adherence interventions, remains high. In both groups of GIVE MOVE, more than 40% of participants had sustained viraemia at 36 weeks despite the use of comparatively well staffed facilities and possible Hawthorne effects of improved adherence or care because of closer observation in a trial setting. A systematic review of viral resuppression after viraemia in individuals with HIV showed even worse outcomes than we observed, with only 31·2% of children and 40·4% of adolescents reaching viral resuppression after enhanced adherence counselling.[30] Our initial assumption that GRT might lead to more informed and effective adherence counselling even in the absence of resistance was not supported by our findings. Baseline characteristics, such as 45% of participants having lost one or both parents, indicate considerable socioeconomic challenges in the trial population. Adolescents with HIV have complex health needs, including psychosocial, familial or provider care, autonomy, treatment self-management, health-service, financial and material, informational, and developmental needs.[31] However, meeting these needs is challenging: a trial in Lesotho designed to address the specific needs of adolescents and young adults with HIV was unable to improve viral suppression.[32] Multifaceted intervention packages combining biomedical, structural, and psychosocial support extending far beyond what is offered in routine enhanced adherence counselling might be required to improve treatment outcomes for these age groups.

The GIVE MOVE trial has several limitations. First, by nature of the intervention, participants and health-care providers were not masked to the study group. Second, if automatic GRT upon detection of viraemia was implemented in routine care, leftover plasma from viral-load testing could be used for GRT upon detection of viraemia, whereas the trial design necessitated obtaining of consent before the subsequent phlebotomy for a new sample for GRT. This aspect delayed decision making and prevented GRT for two-fifths of participants due to viral resuppression. However, a recommendation from the GRT expert committee was still provided. Third, the provision of GRT was operationally challenging and often delayed. Challenges included timely sample transport, reagent stock-outs, instrument breakdowns, and laboratory staff capacity. However, such delays would also be expected upon implementation of GRT in routine care. Fourth, the proportion of primary-endpoint events observed in the GRT and usual care groups was higher than that originally estimated in the sample size calculation. Finally, most participants were classified as being at WHO HIV clinical stage 1 and had no or mild immunosuppression at enrolment, thus our results might not be generalisable to individuals with more advanced HIV disease.

See Online for appendix 4

The trial also has several strengths. GIVE MOVE is the largest trial to test GRT-informed management of viraemia in children and adolescents, and the first in any age group to do so in the era of dolutegravir. The provision of and high adherence to expert recommendations minimised the risk of GRT results not being well understood. The high consistency of findings across sensitivity analyses and subgroups further increases confidence in results.

In conclusion, GIVE MOVE assessed GRT as part of a public health approach. Its findings should neither be extrapolated to settings with the capacity for more individualised care nor hinder innovation to increase access to GRT.[5] However, our findings suggest that in a programmatic setting, broad use of GRT to inform onward care does not substantially improve treatment outcomes for children and adolescents with viraemia. Further research is needed to better support adherence, which we found to be the primary driver of viraemia because most participants in the GRT group with successful GRT had three fully active drugs in their baseline regimen. In addition, for the substantial proportion of individuals with treatment-relevant resistance, better approaches are needed to identify individuals or subgroups who are most likely to benefit from rapid access to GRT.

Contributors

NDL conceptualised the study. NDL and JAB acquired funding. NDL, JAB, TRG, MW, JM, TK, AA, NaT, GJM, and EL designed the study. NDL and JAB carry overall responsibility for the trial. TRG wrote the statistical analysis plan, conducted all preplanned analyses, and is the responsible statistician. JAB and NaT conducted the post-hoc analyses. MB managed the data. All authors had access to the data in the study. TRG, NDL, JAB, and MB accessed and verified the data. NDL, JAB, IKR, EL, JM, TK, TRG, MMH, BPK, and MW formed the steering committee. LK, MI, ABI, KuM, NtT, and TM were site investigators in Lesotho, and EL, BS, KaM, and GJM were site investigators in Tanzania. IKR managed the trial in Lesotho and EL managed the trial in Tanzania. MC, MM, and NK oversaw diagnostics. BM ensured documentation and data quality. IKR, BM, and EM provided extensive operational support. MW, DS, and LT provided additional oversight. JAB and NDL drafted the first version of the manuscript. All authors shared responsibility for the decision to submit for publication.

Equitable partnership declaration

The authors of this paper have submitted an equitable partnership declaration (appendix 4). This statement allows researchers to describe how their work engages with researchers, communities, and environments in the countries of study. This statement is part of *The Lancet Global Health*'s broader goal to decolonise global health.

Declaration of interests

NDL reports having received travel grants to conferences from Gilead Sciences and ViiV Healthcare, and his division received honoraria for consultancies from ViiV Healthcare and for participation in a data safety monitoring board from Pharming. All other authors declare no competing interests.

Data sharing

De-identified participant data will be made publicly available via the data repository, Zenodo (https://zenodo.org/), upon publication. A protocol manuscript has been published[12] and the full trial protocol and statistical analysis plan are available at https://clinicaltrials.gov/study/NCT04233242.

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