Immunological and virological outcomes in children on lamivudine monotherapy: A South African public sector experience

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Background. In resource-limited settings, holding regimens such as lamivudine monotherapy (LAM) have been used to manage HIV-positive children failing combination antiretroviral therapy to mitigate the risk of drug resistance developing, while adherence barriers are addressed or when access to second- or third-line regimens is restricted. South African HIV treatment guidelines previously advocated the use of LAM to manage HIV-infected children with virological failure. However, the outcomes of patients on LAM compared with those who continued on a failing regimen have not been well described.
Objectives. To investigate characteristics of a large cohort of children placed on LAM and their outcomes.
Method. This was a retrospective review of children with virological failure and the documented M184V drug resistance mutation who were placed on LAM v. a control group of children who continued on a failing regimen despite persistent virological failure. Virological and immunological outcomes of LAM were compared with those in patients who remained on a failing regimen.
Results. A total of 179 children were included in the analysis, with 92 in the LAM group and 87 in the control group. The median (interquartile range (IQR)) age at baseline was 9.2 (5.4 - 12) years, the median CD4 count was 384 (184 - 622) cells/μL, and the median HIV viral load was 4.7 (IQR 3.7 - 5.3) $\log_{10}$. Twenty-two children (25.6%) in the LAM group and 15 (17.4%) in the control group experienced immunological deterioration. There was no statistical difference between the two groups with regard to overall time to immunological deterioration (log-rank *p*-value 0.4810).
Conclusion. Given that a higher proportion of children in the LAM group experienced immunological failure, the LAM strategy may be a useful short-term one but should be restricted to children with limited treatment options. Managing children with virological failure will continue to be a challenge until improved adherence strategies are available.

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After the launch of the national antiretroviral treatment (ART) programme in South Africa (SA) in 2004, an estimated 75% of HIV-infected children accessed ART in the public sector by 2016.[1] With this expanding access, maintenance of long-term viral suppression remains a challenge for HIV-infected children.[2,3] Rates of virological failure in the paediatric age group range from 19.3% to >32% in resource-limited settings.[4,5] These rates are higher than those reported in SA, which range from 6% in KwaZulu-Natal Province[6,7] to 15% in Cape Town.[8]

A particular challenge in paediatric patients, in whom ongoing poor adherence is expected, is the increased accumulation of HIV drug resistance mutations.[9-12] In such instances, a holding regimen strategy to 'buy time' while improving adherence has been employed. In SA, this approach employed lamivudine monotherapy (LAM), as the lamivudine-associated M184V mutation is less fit compared with the wild-type virus,[13] and continued maintenance of the M184V mutation may be associated with slower immunological deterioration compared with discontinuing HIV treatment altogether. As the national paediatric antiretroviral guidelines recommended holding strategies for children with ongoing adherence challenges,[14] this was an attractive option for many paediatricians in SA, resulting in a number of studies on the effectiveness of LAM with reports of slower immunological decline with the use of LAM despite the presence of the M184V mutation and high-level resistance to lamivudine and emtricitabine.[15,16] Further support for this treatment strategy stemmed from a number of adult studies reporting improved virological and immunological outcomes in patients on lamivudine or emtricitabine monotherapy compared with continuation on a failing regimen.[17-19] While holding regimens may be easier to administer than combination antiretroviral therapy and have fewer side-effects and a lower risk of emergence of resistance mutation,[19,20] there was insufficient evidence for this approach in children.[17]

Objectives

Our study compared the characteristics and outcomes of paediatric patients placed on LAM against a control group who continued on a failing treatment regimen, to evaluate the appropriateness of the LAM strategy in SA.

Methods

Dr George Mukhari Academic Hospital (DGMAH), an academic hospital in the north of Pretoria, has a busy outpatient paediatric HIV

clinic that was started in 2004. The clinic currently has ~2 200 active patients. It mainly provides outpatient care for HIV-infected children and monitoring of HIV viral loads, CD4 counts and safety bloods, the frequency of which are determined in accordance with the national paediatric antiretroviral guidelines.[14] Paediatricians and registrars, as well as trained nurses, provide care to patients receiving combination ART.

In keeping with the national paediatric antiretroviral guidelines,[14] children with virological failure – defined as a viral load >1 000 copies/mL (3 $\log_{10}$) on two separate occasions – were switched to a new effective regimen. However, when issues of ongoing adherence were identified, the holding regimen of LAM monotherapy was instituted from 2011 to 2016, although some children remained on a failing regimen with no intervention. There were no definitive evidence-based criteria for selection of children to be placed on LAM, and duration on a holding regimen was not defined. However, CD4 counts and HIV viral load measurements were conducted on all children in the two cohort groups every 3 months. Immunological deterioration was defined as the first 30% drop in CD4 count during follow-up, while virological failure was defined as the first viral load >1 000 copies/mL during follow-up.

Study design

A retrospective cohort analysis was conducted using data from medical files of children actively managed at the DGMAH paediatric HIV clinic from 2004 to 2017. Included were all children with a history of a viral load >1 000 copies/mL, HIV-1 genotyping conducted between 2011 and 2016, and evidence of the M184V mutation from the genotype report. Excluded were individuals with: (*i*) evidence of hepatitis B virus infection; (*ii*) follow-up of <6 months; and/or (*iii*) incomplete or missing medical records. The cohort was further refined to include only those who had been placed on LAM and those who despite virological failure had had no regimen switch and remained unchanged on a failing regimen during the study period.

A total of 193 children who fulfilled the inclusion criterion were selected for this study. Of these 193, 102 had received weight band-appropriate dosing of LAM monotherapy. A control group of 91 children without an ART regimen switch despite persistent virological failure was also identified (Fig. 1).

Immunological and virological data collected at the time of ART initiation through 2016 were used as endpoints. For children on LAM monotherapy, immunological deterioration from 6 months following initiation of treatment and over the duration of LAM monotherapy was evaluated. Analysis was conducted on children who received LAM for >12 months. The time of observation of children was from initiation on LAM monotherapy to 12 months of follow-up, whereas for the control group, the time of observation included the first episode of virological failure to ~12 months of follow-up.

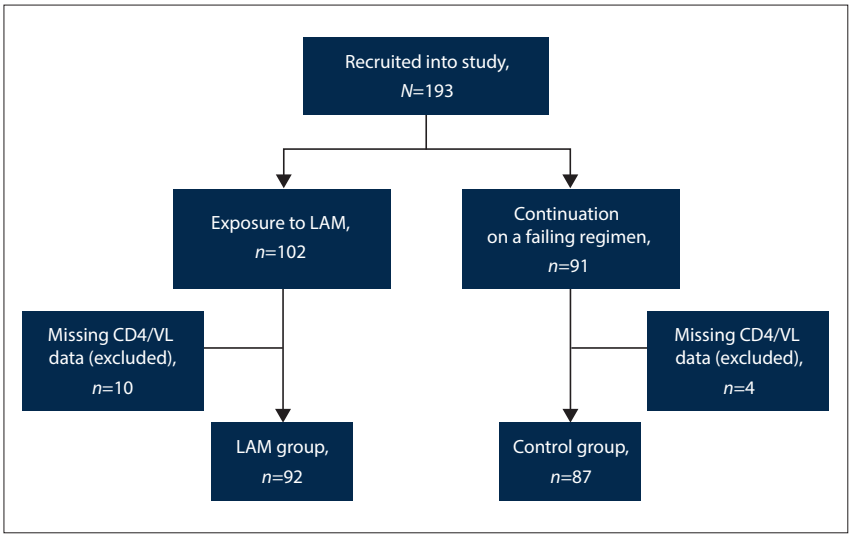

Fig. 1. Selection of patients for the LAM and control groups. (LAM = lamivudine monotherapy; VL = viral load.)

Statistical analysis

The variables available for this analysis included age, gender, World Health Organization (WHO) staging, tuberculosis (TB) treatment at initiation of ART, absolute CD4 count, CD4 percentage and HIV viral load.

Descriptive statistics were determined for continuous measures using medians and interquartile ranges (IQRs), whereas frequencies were determined for categorical measures. HIV viral loads were compared using both the absolute viral load levels and their $\log_{10}$ transformations. Comparison of continuous measures between the LAM and control groups was conducted using the Kruskal-Wallis non-parametric test, with categorical measures compared using the χ^2 statistical test.

Overall time to immunological deterioration was assessed by Kaplan-Meier survival curves and controlled by gender, WHO staging and concurrent TB treatment. The log-rank test was used to evaluate the significance of the difference in survival for selected categorical variables. WHO staging data were stratified as stages 1/2 or stages 3/4. Statistically significant differences between the two groups were noted for each variable if the *p*-value was <0.05. Linear mixed modelling where the dependent variable was either CD4 count or viral load and the month of follow-up was the covariate was implemented to determine the rate of decline or increase over time.

Graphical plots for CD4 count and viral load during follow-up were generated, stratified by treatment group and presented as scatter plots. All statistical analysis was conducted in SAS Enterprise Guide 7.15 (SAS Institute, USA).

Ethical considerations

Ethical approval was granted from the School of Pathology and Preclinical Sciences Research Ethics Committee at Sefako Makgatho Health Sciences University (ref. no. SMUREC/M/30/2017).

Results

Baseline characteristics

A total of 179 children who had at least one immunological or virological measure were included in the analysis. Overall, 14 children (7.8%) had no measurements beyond treatment initiation and were excluded from analysis, leaving 92 children in the LAM group and 87 in the control group.

The overall median (IQR) age of the children in the cohort was 9.2 (5.4 - 12) years. All the children were black Africans and most were South African, with 14 (7.8%) from Zimbabwe. The median baseline CD4 count and HIV viral loads were 384 (184 - 622) cells/μL and 4.7 (3.7 - 5.3) $\log_{10}$, respectively. The characteristics of the study participants are presented in Table 1.

Table 1. Baseline characteristics of the LAM and control groups

Variable	Overall (*N*=179)	Control (*n*=87)	LAM (*n*=92)	*p*-value
Gender, *n* (%)				
Female	76 (42.5)	39 (44.8)	37 (40.2)	0.5328
Male	103 (57.5)	48 (55.2)	55 (59.8)	
WHO stage, *n* (%)				
1	5 (2.8)	4 (4.6)	1 (1.1)	0.0554
2	16 (8.9)	9 (10.3)	7 (7.7)	
3	125 (69.8)	53 (61)	72 (78.2)	
4	33 (18.4)	21 (24.1)	12 (13.0)	
TB treatment, *n* (%)				
Not on treatment	100 (55.9)	51 (58.6)	49 (53.3)	0.4704
On treatment	79 (44.1)	36 (41.4)	43 (46.7)	
Age (months), median (IQR)	*n*=173	*n*=82	*n*=91	<0.0001
	111.0 (64.4 - 146.2)	92.3 (46.8 - 123.4)	133.6 (79.6 - 159.6)	
CD4 count (cells/μL), median (IQR)	*n*=95	*n*=40	*n*=55	0.3351
	384.0 (184.0 - 622.0)	204.5 (36.5 - 541.5)	446.0 (259.0 - 687.0)	
CD4%, median (IQR)	*n*=94	*n*=39	*n*=55	<0.0001
	12.8 (7.0 - 21.5)	8.9 (2.4 - 12.8)	17.2 (11.6 - 22.9)	
Viral load (log_{10}), median (IQR)	*n*=85	*n*=48	*n*=37	0.9189
	4.7 (3.7 - 5.3)	4.8 (3.7 - 5.4)	4.5 (3.4 - 5.2)	

LAM = lamivudine monotherapy; Control = continuation on a failing regimen; WHO = World Health Organization; TB = tuberculosis; IQR = interquartile range.

The median (IQR) age of the LAM group was significantly higher than that of the control group (11.1 years v. 7.7 years; $p<0.0001$). The median CD4 count of the LAM group was 446 (259 - 687) cells/μL and was significantly higher than that of the control group (205 (36.5 - 541.5) cells/μL). Eight children on LAM (8.7%) had an initial CD4 count <350 cells/μL. Most of the children in the LAM group were categorised as WHO stage 3 (78.0%), and 46.7% had been on concurrent TB treatment/ART at initiation.

ART regimen

Of the 179 children in the LAM and control groups combined, 136 (76.0%) were placed on a stavudine/lamivudine and 43 (24.0%) on an abacavir/lamivudine nucleoside reverse transcriptase inhibitor backbone. Sixty-four (35.8%) of the children had efavirenz as the third antiviral agent, with the remaining 115 (64.2%) on boosted lopinavir. Of the 179 children, 51 (28.5%) were failing on the first-line regimen while the remaining 128 (71.5%) were failing on the second-line regimen (Table 2).

Table 2. Combination antiretroviral regimens in the LAM and control groups

ART regimen	LAM (*n*=92), *n* (%)	Control (*n*=87), *n* (%)
d4T/3TC/EFV	10 (10.9)	20 (22.9)
d4T/3TC/LPV/r	60 (65.2)	46 (52.9)
ABC/3TC/EFV	18 (19.6)	16 (18.4)
ABC/3TC/LPV/r	4 (4.3)	5 (5.7)

LAM = lamivudine monotherapy; Control = continuation on a failing regimen; D4T = stavudine; 3TC = lamivudine; EFV = efavirenz; LPV/r = lopinavir/ritonavir; ABC = abacavir.

Outcomes

CD4 count changes

The absolute CD4 count (486 v. 365 cells/μL; $p=0.0003$) and CD4 percentage (18.7% v. 11.0%; $p<0.0001$) were significantly higher at 6 months in the LAM group compared with the control group. The HIV viral load was also significantly higher in the LAM group compared with the control group (4.5 v. 2.5 log_{10}; $p<0.0001$). There were no differences between the groups with regard to absolute CD4 count or CD4 percentage at 12 months. The HIV viral load remained significantly higher in the LAM group compared with the control group (4.6 v. 2.0 log_{10}; $p<0.0001$). Outcomes in the two groups at 6 and 12 months are presented in Table 3.

HIV drug resistance mutations

The M184V mutation was present in all 179 children (100%) and thymidine analogue mutations in 125 with exposure to stavudine (69.8%). For the children with exposure to abacavir, L74V mutation was detected in 8.4% (*n*=15/179). Non-nucleoside reverse transcriptase inhibitor (NNRTI)-resistance mutations were detected in all 64 children with exposure to efavirenz, K103N (*n*=62; 96.8%), V106M (*n*=51; 79.7%), Y181C (*n*=39; 60.9%) and G190A (*n*=37; 57.8%) being the most common mutations. Of the 115 children (64.2%) on boosted lopinavir (LPV/r), 53.0% (*n*=61) harboured major protease resistance mutations. The CD4 count plots during follow-up, illustrating whether they increased or decreased during follow-up, are presented in Fig. 2. The LAM group had a lower CD4 count increase of ~0.27 per month, whereas the control group had a higher increase of ~9.83 per month. The mean CD4 percentage in the LAM group remained generally higher at enrolment and at 6 months, but by 12 months was similar between the two groups.

Immunological decline

Of the children enrolled, 172 of 179 (96.1%) had follow-up data for assessing immunological failure, and included 86 children in each group. There were 22 children (25.5%) who experienced a deterioration in the LAM group and 15 (17.4%) in the control group. The mean (standard error) time to immunological deterioration following enrolment was 219.7 (6.5) days and 300.5 (8.6) days in the LAM and control groups, respectively. There was no difference between the groups with regard to the overall time to immunological deterioration (log-rank *p*-value 0.4810) (Fig. 3).

Table 3. Immunological and virological outcomes in the LAM and control groups at 6 and 12 months

	6 months				12 months			
Variable	**Overall (*N*=179)**	**Control (*n*=87)**	**LAM (*n*=92)**	***p*-value**	**Overall (*N*=179)**	**Control (*n*=87)**	**LAM (*n*=92)**	***p*-value**
CD4 count (cells/μL), median (IQR)	*n*=152 439.5 (276.0 - 691.0)	*n*=71 365.0 (243.0 - 634.0)	*n*=81 486.0 (328.0 - 732.0)	0.0003	*n*=143 475.0 (288.0 - 797.0)	*n*=70 541.5 (287.0 - 870.0)	*n*=73 458.0 (293.0 - 647.0)	0.1352
CD4%, median (IQR)	*n*=150 15.8 (9.1 - 22.1)	*n*=69 11.0 (5.9 - 17.8)	*n*=81 18.7 (12.4 - 24.4)	<0.0001	*n*=142 16.8 (12.5 - 23.6)	*n*=69 16.8 (11.3 - 23.6)	*n*=73 16.2 (12.9 - 23.4)	0.1332
Viral load (copies/mL), median (IQR)	*n*=142 11 076 (190 - 54 038)	*n*=71 326 (19 - 33 000)	*n*=71 30 075 (8 700 - 71 903)	0.7450	*n*=129 6 200 (19.0 - 55 184)	*n*=74 95 (19 - 20 000)	*n*=55 39 577 (5 857 - 132 467)	0.0010
Viral load (log_{10}), median (IQR)	*n*=142 4.0 (2.3 - 4.7)	*n*=71 2.5 (1.3 - 4.5)	*n*=71 4.5 (3.9 - 4.9)	<0.0001	*n*=129 3.8 (1.3 - 4.7)	*n*=74 2.0 (1.3 - 4.3)	*n*=55 4.6 (3.8 - 5.1)	<0.0001

LAM = lamivudine monotherapy; Control = continuation on a failing regimen; IQR = interquartile range.

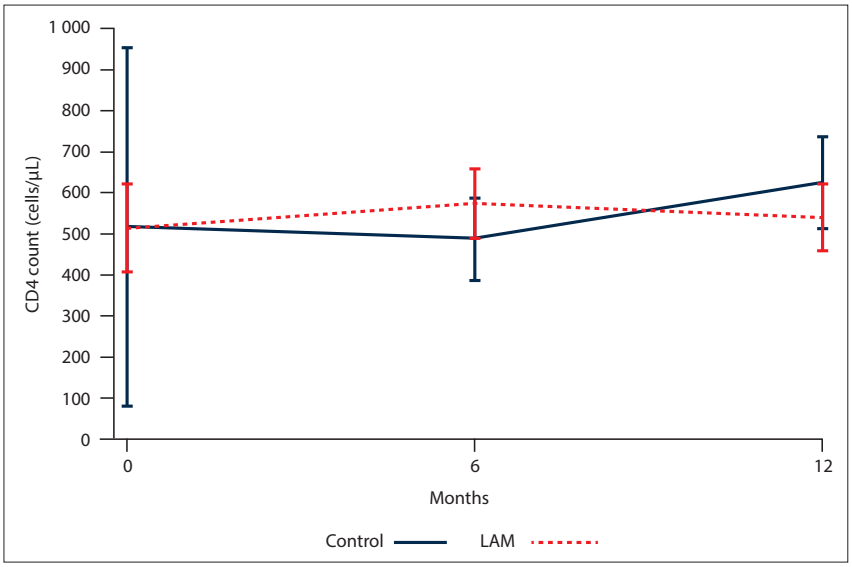

Fig. 2. CD4 counts in the LAM and control groups at 6 and 12 months of follow-up. (LAM = lamivudine monotherapy; Control = continuation on a failing regimen.)

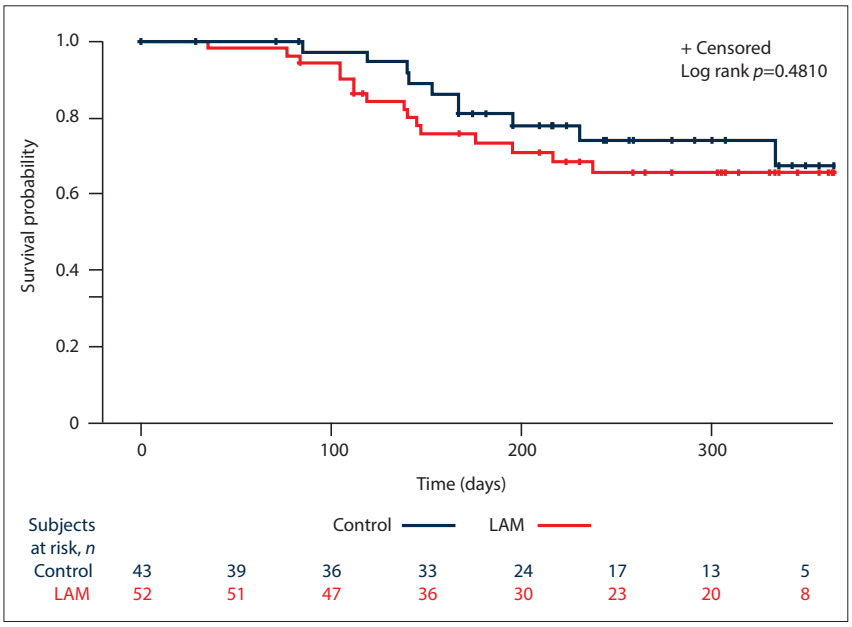

Fig. 3. Time to immunological failure in the LAM and control groups (product-limit survival estimates with number of subjects at risk). (LAM = lamivudine monotherapy; Control = continuation on a failing regimen.)

Further analysis of the time to immunological deterioration, controlling for gender, WHO stage and concurrent TB treatment, yielded no differences between the two groups.

Discussion

Despite significant gains made by SA in terms of access to ART in the paediatric population, challenges pertaining to optimal management strategies for virological failure persist. Management of virological failure in paediatric populations remains a challenge for a variety of reasons, including dependence on the caregiver for administration, poor palatability of drugs, drug-drug interactions, and limited paediatric drug formulations.[21-23]

Several observational studies on the safety and efficacy of paediatric LAM use in SA have shown immunological deterioration, in 39.1 - 71% of patients.[15,16,24] However, it should be highlighted that none of these SA studies includes an appropriate control group. The IMPAACT P1094 study – the only randomised clinical trial (RCT) in children on LAM compared with those continuing a failing PI regimen – reported a >30% decline in CD4 count in 5 children (29%) in the LAM arm and none in the failing regimen arm.[17] In the current retrospective study, the number of children who reached

the predefined endpoint of CD4 count decline >30% was higher in the LAM group (n=22/86; 25.5%) compared with the control group (n=15/86; 17.4%). This finding is consistent with the IMPAACT P1094 RCT,[17] with 25.6% in our cohort from the LAM group experiencing immunological deterioration. Immunological decline was also observed in the control group, contrary to findings from the IMPAACT RCT, in which a >30% decline in CD4 count was not reported. The discrepancy between the control groups in the IMPAACT RCT and our study may be explained by a longer duration on ART in our control group. It is unclear why the majority of children in the LAM group did not experience immunological decline; however, it is worth noting that our definition of decline was quite significant (30% decline) and we may have missed less severe immunological decline. Similarly, it is also unclear why the majority of children in the control group experienced significant improvements in their CD4 counts. The possibility that improved adherence to a potentially more active ART regimen would account for the improvements in CD4 count over the 12-month period cannot be ruled out. It could also reflect improved clinician experience with difficult-to-treat children.

Virological suppression is highly unlikely without combination ART; therefore, as expected, all children placed on LAM remained viraemic during the period of analysis. HIV viral loads were higher in the LAM group compared with the control group (4.6 v. 2.0 $\log_{10}$; p<0.0001). However, the LAM group experienced a slower viral rebound, with only a 0.1 $\log_{10}$ drop from 6 to 12 months compared with the control group, in which there was a 2.8 $\log_{10}$ drop.

The present study represents one of the largest SA cohorts of children on LAM, adding to the evidence base on the effectiveness of this strategy. However, the differences in characteristics between the LAM and control groups have made it difficult to compare the outcomes between the two groups at 6 and 12 months. Selection bias is a consideration in this study, as a safety criterion used by clinicians at the HIV clinic for placement of children on LAM was a CD4 count ≥350 cells/μL. Children were also monitored closely, with monthly clinic visits, CD4 count monitoring at 3-monthly intervals, and adherence counselling. It is therefore possible that the higher CD4 count in the LAM group compared with the control group at 6 months is attributable to the higher CD4 count at baseline rather than treatment received by the children in each group. Additionally, there are no data on adherence, as such data are not routinely included in the medical record. The effect of adherence on immunological outcomes in LAM-treated children therefore cannot be assessed. Our findings may also not be generalisable to other settings.

Conclusion

Despite improvements in access to ART and management of HIV-infected children, virological failure remains a challenge. Enhanced adherence measures are essential to support HIV-infected children and minimise the emergence of HIV drug resistance, which creates significant challenges to achieving fully suppressive regimens. Although the LAM strategy is associated with immunological deterioration, it continues to have a place in the management of children with adherence challenges. However, it should be administered for brief periods while efforts are underway to improve adherence. There remains an urgent need for better paediatric treatment options in addition to improved adherence strategies.

Declaration. The research for this study was done in partial fulfilment of the requirements for ZNM's PhD (Virology) degree at the Sefako Makgatho Health Sciences University.

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Conflicts of interest. None.

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