HHS Public Access

Author manuscript

Pediatr Infect Dis J. Author manuscript; available in PMC 2023 July 10.

Published in final edited form as:

Pediatr Infect Dis J. 2023 July 01; 42(7): 573–575. doi:10.1097/INF.0000000000003906.

Implementation and Uptake of Raltegravir Granules in Newborns Diagnosed With HIV Through Birth Testing in Maternity Settings in Zimbabwe During the COVID-19 Pandemic

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Abstract

Zimbabwe introduced raltegravir (RAL) granules at 14 facilities providing point-of-care HIV birth testing, aiming to initiate all newborns with HIV on a RAL-based regimen. From June 2020 to July 2021, we tested 3172 of the 6989 (45%) newborns exposed to HIV; we diagnosed 59(2%) with HIV infection, of whom 27 (46%) initiated RAL. The SARS-CoV-2 coronavirus disease pandemic exacerbated supply chain and trained provider shortages, contributing to low birth testing, RAL uptake and 6-month viral load testing.

Keywords

raltegravir; neonatal; Zimbabwe; HIV

Zimbabwe had an estimated 79,000 children <15 years living with HIV in 2020.[1] Despite the services to prevent perinatal transmission of HIV since early 2000, approximately 5100 new infections occurred in children in Zimbabwe in 2020.[1] Early diagnosis and rapid antiretroviral treatment (ART) initiation are recommended to reduce the high risk of mortality in untreated infants and children.[2] In 2017, Zimbabwe introduced point-of-care (POC) early infant diagnosis (EID) at birth for newborns exposed to HIV, reducing the

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The authors have no conflicts of interest to disclose.

time to results receipt and treatment initiation for infected infants.[3] Because of the limited availability of ART regimens approved for use in neonates (age <4 weeks) diagnosed with HIV, the first-line regimen used in neonates was zidovudine, also known as azidothymidine (AZT)/lamivudine (3TC) + nevirapine (NVP).

Due to the high rates of resistance to nonnucleoside reverse transcriptase inhibitors, such as NVP, in 2019, Zimbabwe adopted World Health Organization guidance to replace NVP-based ART regimens with raltegravir (RAL)-based regimens paired with AZT/3TC as the first choice for neonates living with HIV (NLHIV). During the first 28 days of life, with programmatic rollout planned for early 2020.[4,5] The use of RAL granules is complex and requires several dosing changes in the first 28 days of life and regimen switching on day 28.[6] The Faith-Based Action for Scaling-up Testing and Treatment for the Epidemic Response project and Ministry of Health and Child Care collaborated to introduce RAL-based ART for neonates diagnosed with HIV at birth. We describe the implementation and lessons learned from the roll-out of neonatal RAL-based ART during the SARS-CoV-2 coronavirus disease (COVID-19) pandemic.

MATERIALS AND METHODS

This retrospective longitudinal study was implemented through the Faith-Based Action for Scaling-up Testing and Treatment for the Epidemic Response project support from June 2020 to June 2021 in 14 health facilities in Zimbabwe that were purposively selected for the introduction of RAL granules because of high volumes of infants exposed to HIV and existing capacity for POC HIV birth testing. These 14 facilities were part of 41 hospitals implementing POC EID since 2017.

In June 2020, healthcare workers (HCWs) at the 14 facilities were trained on RAL use and on counseling caregivers on the preparation and administration of RAL to NLHIV[6] Caregivers were instructed to return at 7 and 28 days after birth for routine newborn and HIV care. This included weight checks to monitor growth and subsequent adjustment of RAL dosage, as well as switching RAL granules to lopinavir/ritonavir (LPV/r) or pediatric dolutegravir (pDTG) (available April 2021) in combination with an abacavir and 3TC backbone at age 28 days.

The study population included all infants born to mothers living with HIV identified at project sites from June 2020 to June 2021. From April to July 2021, trained research assistants abstracted testing and ART outcome data from standard facility-based tools and registers. Abstracted elements included demographic data, POC EID birth testing, HIV diagnosis and ART initiation. ART follow-up data for up to 6 months of life or up to the last date of data collection (July 4, 2021) were captured from the Ministry of Health and Child Care HIV Care Register. Research assistants received COVID-19 mitigation training and were provided with personal protective equipment.

De-identified data were directly entered into a Microsoft Access database using a password-protected laptop. Data analysis was done using STATA version 16, with descriptive summary

statistics displayed. When appropriate, comparisons used the Fisher exact test for categorical variables and Wilcoxon rank sum test for continuous variables, with 5% significance level.

The study protocol was reviewed and approved by the Research Council of Zimbabwe, the Medical Research Council of Zimbabwe (MRCZ/A/2343) and the Advarra's Institutional Review Board based in United States. This activity was reviewed by the United States Center for Disease Control and Prevention and was conducted consistent with applicable federal law and the Center for Disease Control and Prevention policy.

RESULTS

Overall, of the 6989 newborns exposed to HIV at project sites, 3204 (45.8%) received POC EID testing in the first 4 weeks of life (Fig. 1); 97.9% (n = 3137) within the recommended range of 0–3 days after birth, 1.4% (n = 46) between 4 and 7 days after birth and 0.7% (n = 21) between 8 and 28 days.

Among these 3204 infants, 3169 infants had a test result, including 59 [1.9% (95% confidence interval: 1.4–2.4)] with a positive result. Of these, 46 (78.0%) were initiated on ART; the rest were either not initiated on ART (n = 7) or had no documentation of ART initiation (n = 6). Four children were not initiated on ART because stockout of AZT/3TC prevented provision of a full ART regimen. All identified neonates not initiated on ART were identified with HIV within 72 hours of birth.

Of the 46 infants initiated on ART within 28 days of life, 27 (58.7%) received RAL-based regimens (AZT/3TC + RAL in all cases) and 19 (41.3%) received non-RAL-based regimens (AZT/3TC + NVP, n = 9; abacavir/3TC + LPV/r, n = 8; AZT/3TC + LPV/r, n = 1; abacavir/3TC + pDTG, n = 1). Although LPV/r is not recommended within 2 weeks after birth, 3 infants were initiated on LPV/r within this time window. The infant on the pDTG regimen was initiated 4 days after birth, although pDTG is only recommended for infants ≥4 weeks of age. Infants initiated on RAL were initiated significantly earlier than those initiated on other ART regimens (median, 4 days vs. 6 days; $P = 0.03$).

Data on the switch from RAL to non-RAL regimen at 28 days of life was available for 23 of the 27 (85.2%) children who received RAL granules during implementation; 18 (78.3%) switched to a non-RAL regimen at 28 days, of whom 12 switched to a national guideline-approved regimen. However, 6 infants received AZT/3TC + LPV/r, which is not a nationally recommended regimen.

Weight was recorded at day 7 for only 10 of the 27 (37.0%) infants on RAL and for 6 of 19 (31.6%) still in care at 28 days. Among the 29 of the 46 children on ART who reached the 6-month time point at the end of data collection (15/27 on RAL), only 10 of the 29 (34.5%) had a clinical record available on site [6/15 (40.0%) on RAL].

Viral load (VL) results were largely missing; only 2 infants had a VL result at 6-months, both collected from clinics with onsite POC VL and both showed viral suppression (<1000 copies/mL). The VL result for the child who received RAL granules was undetectable; the results for the child who did not receive RAL was 87 copies/mL. Although one child died

soon after birth and before ART initiation, no child deaths were reported among the 46 on ART. No adverse drug events were documented.

DISCUSSION

Literature on the feasibility of using RAL granules in NLHIV is limited. Mills et al[7] described an iterative participative process to optimize pediatric RAL packaging and instructions for use involving untrained lay individuals with varying levels of health literacy, health care professionals and health literacy experts. A qualitative study among HCWs and caregivers from a middle-income setting (South Africa) showed that despite the complexity of granule preparation for oral suspension, with practice, this formulation was acceptable and feasible,[8] which was also supported by an accompanying qualitative analysis of feedback on RAL granule use from caregivers and HCWs at 8 of our 14 study facilities.[9]

This study is the first to describe the programmatic rollout of RAL granules for NLHIV in a low-resource setting. Lower than expected birth testing uptake and RAL usage were observed; less than half of the eligible neonates accessed POC EID, while half of those diagnosed with HIV received RAL granules. Low uptake of both birth testing and RAL usage was likely due to the unforeseen COVID-19-related disruptions and challenges faced by the health care facilities and clients reported by the project team, as supported by the accompanying qualitative findings.[9]

Global and national COVID-19-related travel restrictions delayed manufacturer deliveries and in-country distribution, which impacted the availability of POC EID testing cartridges, RAL granules and pediatric AZT/3TC. The short shelf-life (9 months) of POC cartridges was an additional challenge, as was appropriate stock management of POC cartridges and antiretroviral drugs. Pediatric antiretroviral drugs are used infrequently, making forecasting and supply chain management critical to ensuring their availability and utilization before expiration.

A second challenge was the shortage of trained HCWs due to strikes and staff turnover. Staff reassignment and facility space redistribution to support COVID-19-related activities resulted in some staff not receiving training on POC EID or updated neonatal ART guidelines. COVID-19-related travel restrictions also limited in-person mentorship and supervision visits. Additionally, high staff attrition led to work overload for remaining staff and reprioritization to other medical emergencies and COVID-19. Ongoing and future COVID-19 disruptions will benefit from innovative approaches to mitigate the impact. Task shifting has been successfully used to address staff shortages and improve access to POC EID testing in similar settings.[10] It is critical for program managers to identify and address service training gaps to facilitate successful HCW task-shifting.

A third challenge was retrospective data abstraction of data points not recorded or not maintained in facility registers. For example, medication information was only documented in the clients' take-home medical booklet. Absence of facility-based documentation made it impossible to assess HCW ability to correctly prescribe RAL granule dosages. Facility-maintained documentation of infant weight and RAL dosage are needed for monitoring ART

prescription accuracy, nationally. Another noted documentation gap was routine 6-month VL after ART initiation. Most infants in this study did not have a documented 6-month VL result. Long VL result turnaround time (6 months in 2018)[11] may have been exacerbated during COVID-19; there was no clear facility-maintained documentation of VL sample collection date or anticipated VL result return. More data are needed on VL outcomes in infants who received RAL granules to better understand the real-world effectiveness and whether drug resistance is acquired during neonatal RAL-based ART that impacts virologic success of subsequent preferred DTG-based ART. Incomplete documentation may have led to underestimates of the proportion of children in care and treatment at 6 months; better routine data systems for longitudinal monitoring of NLHIV are needed.

Finally, we acknowledge that this study focused on the uptake of RAL for infants diagnosed with HIV infection within the first 28 days of life and did not assess outcomes for testing and treatment initiation beyond the age of 4 weeks.

In summary, despite low coverage of birth testing, almost half of the identified neonates diagnosed with HIV at study sites were initiated on RAL granule-based regimens, and 78% of those with 1-month follow-up were successfully transitioned to a non-RAL-based regimen at 28 days. COVID-19 negatively impacted the healthcare workforce, supply chain management and documentation of routine services, all of which influenced RAL granule implementation and this retrospective study's ability to fully identify the various barriers to POC birth testing and neonatal treatment initiation. As continued implementation and scale-up of RAL and other neonatal and infant ART such as pDTG is considered, addressing gaps to ensure birth testing of all eligible neonates, careful follow-up of test results, prompt ART initiation, appropriate dosing, 6-month VL testing and better documentation of all these steps, will be critical.

Acknowledgments

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the funding agencies.

This research has been supported by the President's Emergency Plan for AIDS Relief (PEPFAR) through the United States Centers for Disease Control and Prevention under the terms of grants number NU2GGH001463.

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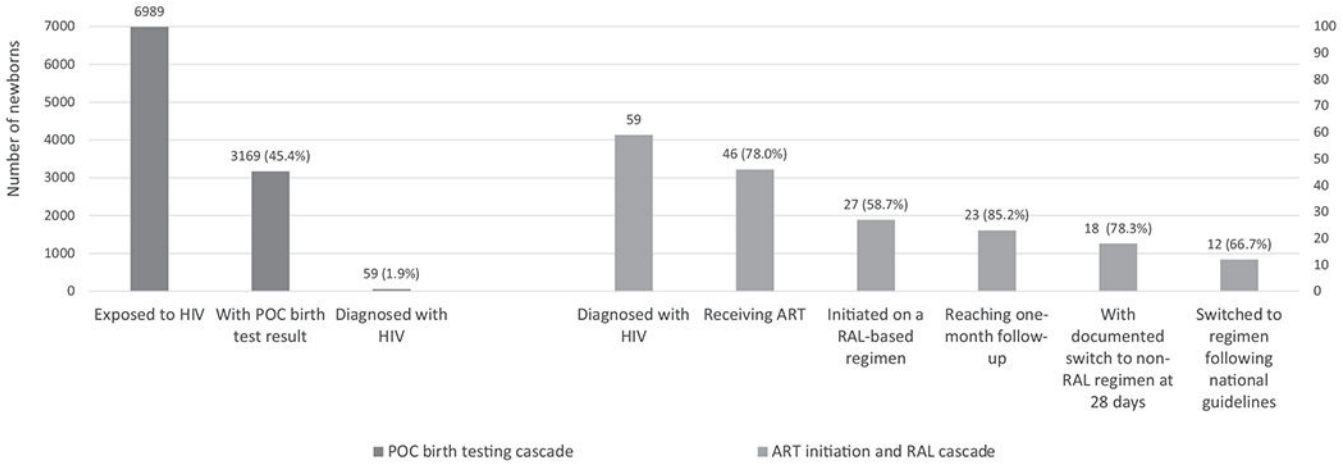

FIGURE 1.

Point-of-care birth testing, ART initiation and RAL treatment cascade; N = 6989 neonates exposed to HIV in 14 health facilities in Zimbabwe.