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Recent trends in adult and pediatric antiretroviral therapy monitoring and failure

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International Epidemiology Databases to Evaluate AIDS – Asia-Pacific

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Abstract

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Author contributions

DCB conceived the concept, carried out the analysis, and led the manuscript; VTA, NK, IA, TS, KHT, AA, JR and AK provided input to the design of the analysis and led data collection; All authors helped draft the manuscript and have read and approved the final submission.

Objective: To assess recent trends in the monitoring of antiretroviral therapy (ART) and detection of ART failure in adult and pediatric HIV clinics.

Methods: We used data collected from 21 adult and 17 pediatric sites (across 13 and 6 countries/territories, respectively) in the International Epidemiology Databases to Evaluate AIDS – Asia-Pacific cohort. ART failure was defined as viral, immune, or clinical consistent with WHO guidelines.

Results: A total of 8,567 adults and 6,149 children contributed data. Frequency of CD4 count monitoring declined between 2010-2019 among adult sites (from 1.93 to 1.06 tests/person/year, a 45.1% decline) and pediatric sites (from 2.16 to 0.86 tests/person/year, a 60.2% decline) while rates of viral load monitoring remained relatively stable. The proportion of adult and pediatric treatment failure detected as immune failure declined (from 73.4% to 50.0% and from 45.8% to 23.1%, respectively) while the proportion of failure detected as viral failure increased (from 7.8% to 25.0% and from 45.8% to 76.9%, respectively). The proportion of ART failure detected as clinical failure remained stable among adult and pediatric sites. The largest shifts in ART monitoring and failure type occurred in lower middle-income countries.

Conclusion: Although viral failure in our Asian cohort now comprises a larger portion of ART failure than in prior years, the diagnostic characteristics of immune and clinical failure, and recommendations on their management, remain important inclusions for regional ART guidelines.

Keywords

HIV; Antiretroviral therapy; Viral load; CD4; Treatment failure; Asia

INTRODUCTION

An important goal of antiretroviral therapy (ART) is the sustained suppression of HIV. Low viral burden substantially reduces the risk of immune and clinical failure,^{1,2} both advanced states of treatment failure that tend to occur after viral non-suppression and lead to a poor clinical prognosis.³⁻⁸ Early detection of viral proliferation allows ART adherence issues to be addressed promptly thereby reducing the likelihood of antiretroviral resistance and retaining second and third line options.^{4,9-11}

Despite providing superior health outcomes, viral load monitoring is more expensive than monitoring for immune or clinical ART failure. CD4 cell count monitoring for detection of immune failure has historically been favoured. However, global access to viral load testing has increased substantially over the past decade due to changes in HIV policy and guidelines, including recommendations to reduce the frequency of CD4 testing, and the decreasing price of viral load monitoring.¹² Although this does not appear to have reduced rates of viral non-suppression over time,¹² rates of ART failure have declined,^{13,14} indicating viral failure may comprise a larger portion of treatment failure than in past years. This has important implications for future policy and guidance on the management of ART failure.

The aim of this analysis was to assess recent trends in the monitoring of ART and detection of ART failure in adult and pediatric HIV clinics in Asia.

METHODS

Study population

We used adult and pediatric data from the International Epidemiology Databases to Evaluate AIDS – Asia Pacific (IeDEA-AP) cohort. Both the adult and pediatric IeDEA-AP cohorts have been described elsewhere.^{15–17} Briefly, the adult IeDEA-AP cohort is a prospective observational database involving 21 sites which began enrolling individuals receiving HIV care at major urban referral centres in 2003. The pediatric IeDEA-AP cohort is also a prospective HIV observational database. It involves 17 major pediatric centres that have been contributing data since 2008. There are seven clinics in the IeDEA-AP network that contribute to both adult and pediatric databases. Adult and pediatric clinics in the IeDEA-AP network generally do not have a strict age restriction. Nevertheless, pediatric sites tend to care for patients <18-years-old and adult clinics tend to care for patients 18-years-old. Data collected in the adult and pediatric cohorts includes information on participant demographics, laboratory results, clinical diagnoses, and ART use. Both cohorts perform six-monthly data transfers from clinic sites to the regional data centre at the Kirby Institute. Our study population included participants in the March 2020 IeDEA-AP cohort data transfers who had been using ART for 6 months

Ethical approval

Adult and pediatric IeDEA-AP cohorts have received approval from the human research ethics committees at participating sites, the Kirby Institute, and the co-ordination center at TREAT Asia/amfAR. Participating clinics follow local guidelines and regulations regarding patient consent.

Outcomes and definitions

Rates of viral load and CD4 monitoring were calculated for each participant as the number of measurements in a calendar year over the total follow up time accumulated in that year.

ART failure was defined as viral, immune, or clinical failure in the 6 months leading up to an antiretroviral drug class change or death. First, second and third episodes of ART failure were included in our analyses and individuals could contribute up to one failure for each.

Our definitions of viral, immune, and clinical failure followed recommendations described in recent World Health Organization (WHO) guidelines.^{18,19} Table S1 describes our definitions in detail. Where an individual had evidence of multiple types of failure during a single episode of failure (i.e., involving one episode of a drug class change or death), priority was given to clinical, immune, then viral failure, in that order. This is because clinical failure typically follows immune failure which typically follows viral failure.³ We also evaluated viral load measurements taken within 6 months of individuals developing immune or clinical failure, and CD4 measurements taken within 6 months of individuals developing clinical failure.

Statistical analysis

We calculated the mean per patient viral load and CD4 monitoring frequency each calendar year, by adult/pediatric site and by country income status. Annual proportions of viral, immune, and clinical ART failure were calculated as the number of viral, immune, or clinical failures divided by the total number of failures in the year. Annual proportions of first, second, and third ART failure were calculated as the number of first, second, and third failures divided by the total number of failures in the year. We evaluated calendar year trends in ART failure proportion, by adult/pediatric site and by country income status. Bivariate linear regression was used to estimate, and calculate the statistical significance of, annual changes in mean viral load and CD4 monitoring frequency, proportion of total failures detected as viral, immune, and clinical failure, and proportion of total failures that were a first, second, and third episode. All statistical analyses were conducted using Stata 16 (Stata Corp., College Station, Texas).

RESULTS

Adult site characteristics

Table S1 shows that among the 21 adult sites, 7 (33.3%), 9 (42.9%) and 5 (23.8%) were situated in lower middle, upper middle and high-income countries, respectively. Eighteen (85.7%) were public facilities and 17 (81.9%) had an academic affiliation. Most (42.9%) sites served an adult patient population of between 1,000-5,000. A total of 8,567 individuals contributed data to our adult analyses.

CD4 and viral load monitoring in adults

Figure 1A and Table S2 show that, among adult sites, the mean rate of viral load monitoring declined from 1.46 tests/adult/year in 2010 to 1.22 tests/adult/year in 2019, a 16.4% decline at 0.02 tests/adult/calendar year ($p=0.05$). Over the same period, the mean rate of CD4 monitoring declined from 1.93 tests/adult/year in 2010 to 1.06 tests/adult/year in 2019, a 45.1% decline at 0.10 tests/adult/calendar year ($p<0.01$).

Figure 2A–C and Table S2 show the decline in viral load monitoring rate was driven by a reduction in monitoring among sites situated in upper middle-income countries (18.4% decline at 0.04 tests/adult/calendar year, $p=0.01$). Declines in CD4 monitoring were significant in sites from each country income status (lower middle, 75.9% decline at 0.18 tests/adult/calendar year, $p<0.01$; upper middle, 33.3% decline at 0.08 tests/adult/calendar year, $p<0.01$; high, 17.4% decline at 0.06 tests/adult/calendar year, $p=0.01$).

Antiretroviral treatment failure in adults

Figure 3A and Table S3 show that the proportion of ART failure detected as viral failure among adults increased from 7.8% in 2010 to 25.0% in 2019 at a rate of 1.9% per calendar year ($p=0.04$). Over the same period, the proportion of ART failure detected as immune failure dropped from 73.4% to 50.0% at a mean decline of 2.32% per calendar year ($p=0.04$) and the proportion of ART failure detected as clinical failure remained stable between approximately 10-20% each year ($p=0.62$).

Figure 4A–C and Table S3 show the only significant changes in the proportion of ART failure attributable to viral or immune failure occurred among sites situated in lower middle-income countries. Among these sites, the proportion of ART failure detected as viral failure increased from 11.1% in 2010 to 33.3% in 2019 at a mean increase of 3.00% per calendar year ($p<0.01$). Over the same period, the proportion of ART failure detected as immune failure decreased from 55.6% to 33.3% at a mean decline of 2.72% per calendar year ($p=0.06$).

Among 108 adults who developed immune failure and had a recent viral load, 63 (58.3%) had a viral load >1000 copies/ml. In 25 adults who developed clinical failure and had a recent viral load, 7 (28.0%) had a viral load >1000 copies/ml. Among 33 adults who developed clinical failure and had a recent CD4 count, 8 (24.2%) had a CD4 <100 cells/ mm^3 .

Over the duration of the study period, the proportions of first, second, and third ART failure among adults were 80.1%, 16.6%, and 3.3%, respectively. These proportions were similar from year to year and across sites from lower middle, upper middle, and high-income countries (Figure S1, Figure S2, and Table S4). Although, the proportion of second ART failure among sites from high income countries declined by a mean of 3.44% per calendar year between 2010 and 2018 ($p<0.01$).

Pediatric site characteristics

Table S1 shows that among the 17 pediatric sites, 6 (35.3%) and 11 (64.7%) were situated in lower middle and upper middle-income countries, respectively. No pediatric sites were based in high-income countries. Sixteen (94.1%) sites were public facilities, and all had an academic affiliation. The vast majority (14; 82.4%) of sites served a pediatric patient population of $<1,000$. A total of 6,149 individuals contributed data to our pediatric analyses.

CD4 and viral load monitoring in children

Figure 1B and Table S2 show that, among paediatric sites, the mean rate of viral load monitoring remained stable at approximately 1 test/child/year between 2010-2019 (mean decline of 0.02 tests/child/calendar year, $p=0.24$). Over the same period, the mean rate of CD4 monitoring declined from 2.16 tests/child/year in 2010 to 0.86 tests/child/year in 2019, a 60.2% decline at 0.16 tests/child/calendar year ($p<0.01$). The mean decline in CD4 monitoring was significant among sites from both lower middle and upper middle-income countries (a 90.3% decline at 0.20 tests/child/calendar year, $p<0.01$ and a 20.2% decline at 0.09 tests/child/calendar year, $p<0.01$, respectively; Figure 2D–E and Table S2).

Antiretroviral treatment failure in children

Figure 3B and Table S3 show that, between 2010-2019 among pediatric sites, the proportion of ART failure detected as viral failure increased from 45.8% to 76.9% at a mean increase of 2.92% per calendar year ($p<0.01$). Over the same period, the proportion of ART failure detected as immune failure dropped from 45.8% to 23.1% at a mean decline of 2.31% per calendar year ($p<0.01$) and the proportion of ART failure detected as clinical failure remained stable between 0-10% ($p=0.10$).

Figure 4D–E and Table S3 show the largest changes in the proportion of ART failure attributable to viral, immune and clinical failure occurred at sites situated in lower middle-income countries. Among these sites, the proportion of ART failure detected as viral failure increased from 36.7% in 2010 to 62.5% in 2019 at a mean increase of 4.59% per calendar year ($p=0.02$). Over the same period, the proportion of ART failure detected as immune failure decreased from 50.0% to 37.5% at a mean decline of 3.17% per calendar year ($p=0.06$) and the proportion of ART failure detected as clinical failure decreased from 13.3% to 0.0% at a mean decline of 1.42% per calendar year ($p=0.04$).

Among 98 children who developed immune failure and had a recent viral load, 85 (86.7%) had a viral load >1000 copies/ml. In 15 children who developed clinical failure and had a recent viral load, 12 (80.0%) had a viral load >1000 copies/ml. Among 27 children who developed clinical failure and had a recent CD4 measurement, 12 (44.4%) had a CD4 level consistent with immune failure.

Over the duration of the study period, the proportions of first, second, and third ART failure among children were 77.9%, 17.8%, and 4.3%, respectively. These proportions were similar from year to year and across sites from lower middle and upper middle-income countries (Figure S1, Figure S2, and Table S4).

DISCUSSION

Rates of CD4 monitoring declined considerably after 2010 among adult and pediatric sites in our Asia-Pacific HIV cohort, while rates of viral load monitoring remained stable. In line with these changes, and consistent with viral load testing being the most sensitive method of diagnosing ART failure, the proportions of adult and pediatric treatment failure detected as immune failure declined substantially while the proportions of treatment failure detected as viral failure increased. The proportion of ART failure detected as clinical failure remained stable among adult and pediatric sites. The largest shifts in ART monitoring and failure detection occurred among sites situated in lower middle-income countries.

HIV guidelines now firmly recommend initiation of ART regardless of CD4 cell count, and prioritisation of viral load monitoring over CD4 or clinical monitoring.^{18,19} Early ART leads to better health outcomes than delayed ART.²⁰ Strong evidence from the Asia-Pacific region shows that regular CD4 monitoring is unnecessary among adults and children with viral suppression on ART due to their very low risk of immune or clinical treatment failure.^{1,2} It was expected that we would see a decline in CD4 monitoring over time in our analysis. However, we also expected an increase in viral load monitoring frequency. Instead, rates remained stable over time among both adult and pediatric sites. In fact, among adult sites in upper middle-income countries viral load monitoring rates declined slightly. This could be representative of more effective ART regimens,¹⁹ and a maturing HIV patient population²¹ that has become comfortable with ART overtime resulting in less frequent laboratory monitoring. Although, difficulty accessing affordable viral load testing materials and technology remains a significant issue in some settings.²²

Despite adult and pediatric sites having an overall decrease in the proportion of ART failure detected as immune failure and an increase in the proportion of ART failure detected as viral failure, both mainly attributable to changes in lower middle-income countries, the overall proportion of ART failure detected as clinical failure remained relatively stable. Further investigation of this finding may be warranted to ensure HIV treatment centres in the region are not oversimplifying ART laboratory monitoring in response to recent guideline changes encouraging greater efficiency.^{18,19,23}

There are several limitations to this analysis. IeDEA-AP represents only a sample of HIV treatment clinics in the Asia-Pacific. We acknowledge that there is substantial intra-regional and inter-ethnic variation across the region which may limit the generalizability of our findings. Our data are from HIV referral centres where patient characteristics may not be representative of the national HIV programmes within which the referral centres operate. The declining rate of ART failure over time among the IeDEA-AP cohort¹³ meant our proportion of failure calculations in later years of the study period tended to be impeded by a low denominator.

Ideally, all ART failures would be detected at the stage of viral failure so that the adverse prognoses associated with immune and clinical could be avoided. This study indicates progress is being made toward that vision in the Asia-Pacific region, particularly among the pediatric HIV population. Nevertheless, the diagnostic characteristics of immune and clinical failure, and recommendations on their management, remain key inclusions for regional ART guidelines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Competing interests

DCB has received research funding from Gilead Sciences and is supported by a National Health and Medical Research Council Early Career Fellowship (APP1140503); All other authors report no potential competing interests.

Data availability

Data were collected as part of a regional cohort collaboration. The cohort collaboration has data-sharing policies that were approved by the corresponding IRB and specify that both

internal and external investigators are subject to a formal process to request access to the data through submission of a concept sheet that adheres to these policies. This study was conducted under these policies, and data will only be available upon request for researchers who meet the criteria for access to confidential data. Interested individuals should contact Boondarika Petersen (tor.nakornsri@treatasia.org).

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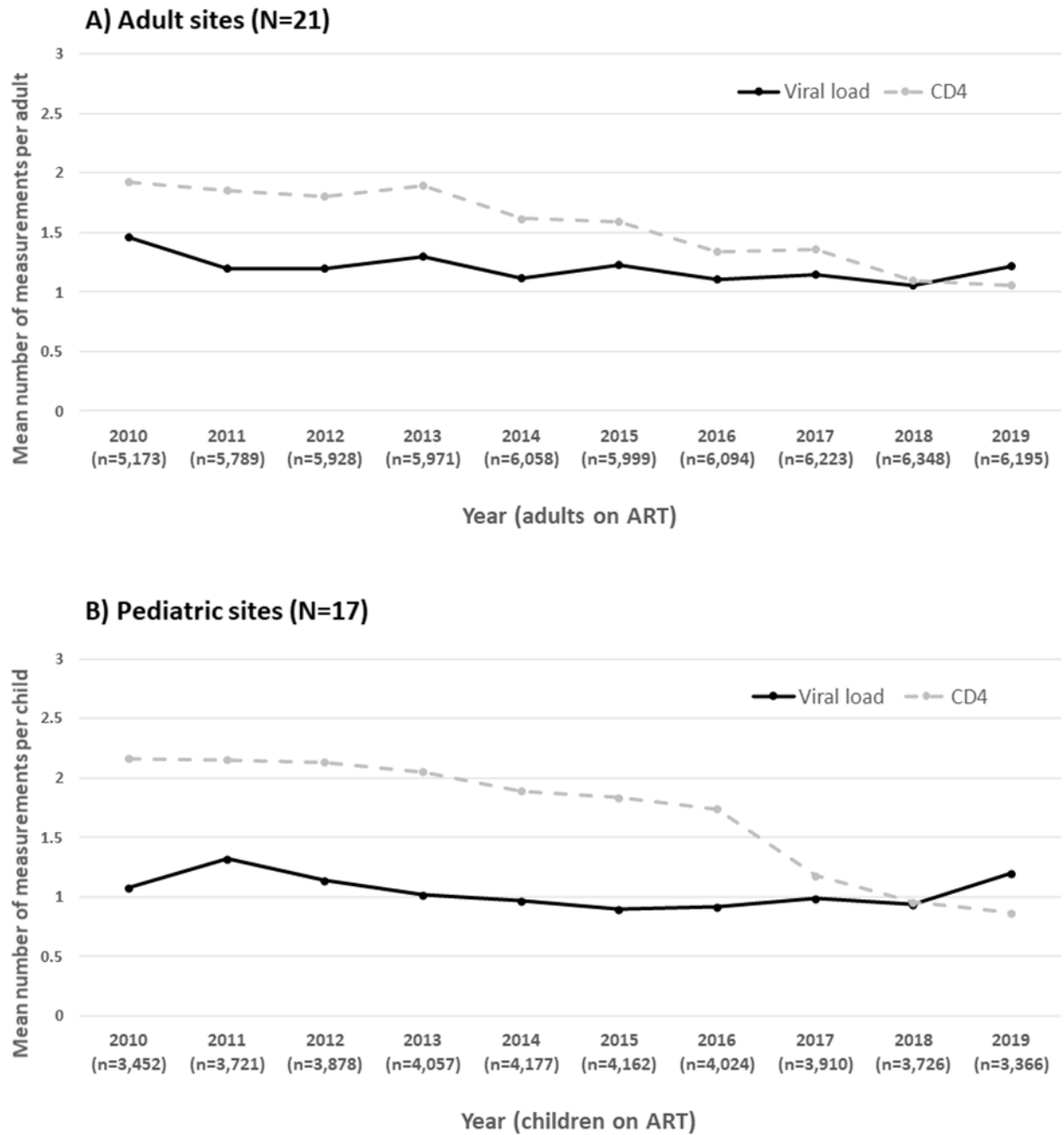


Figure 1.
Calendar year trends in HIV viral load and CD4 cell count monitoring

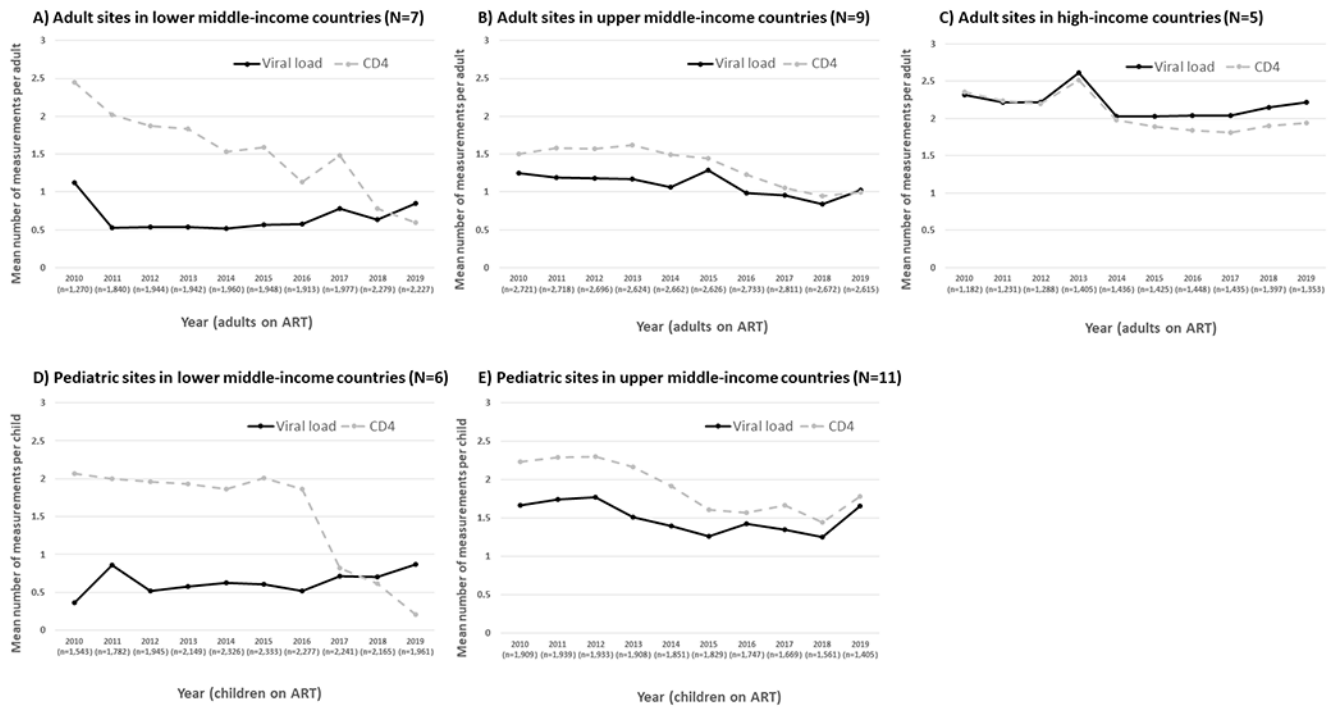


Figure 2. Calendar year trends in HIV viral load and CD4 cell count monitoring by country income status

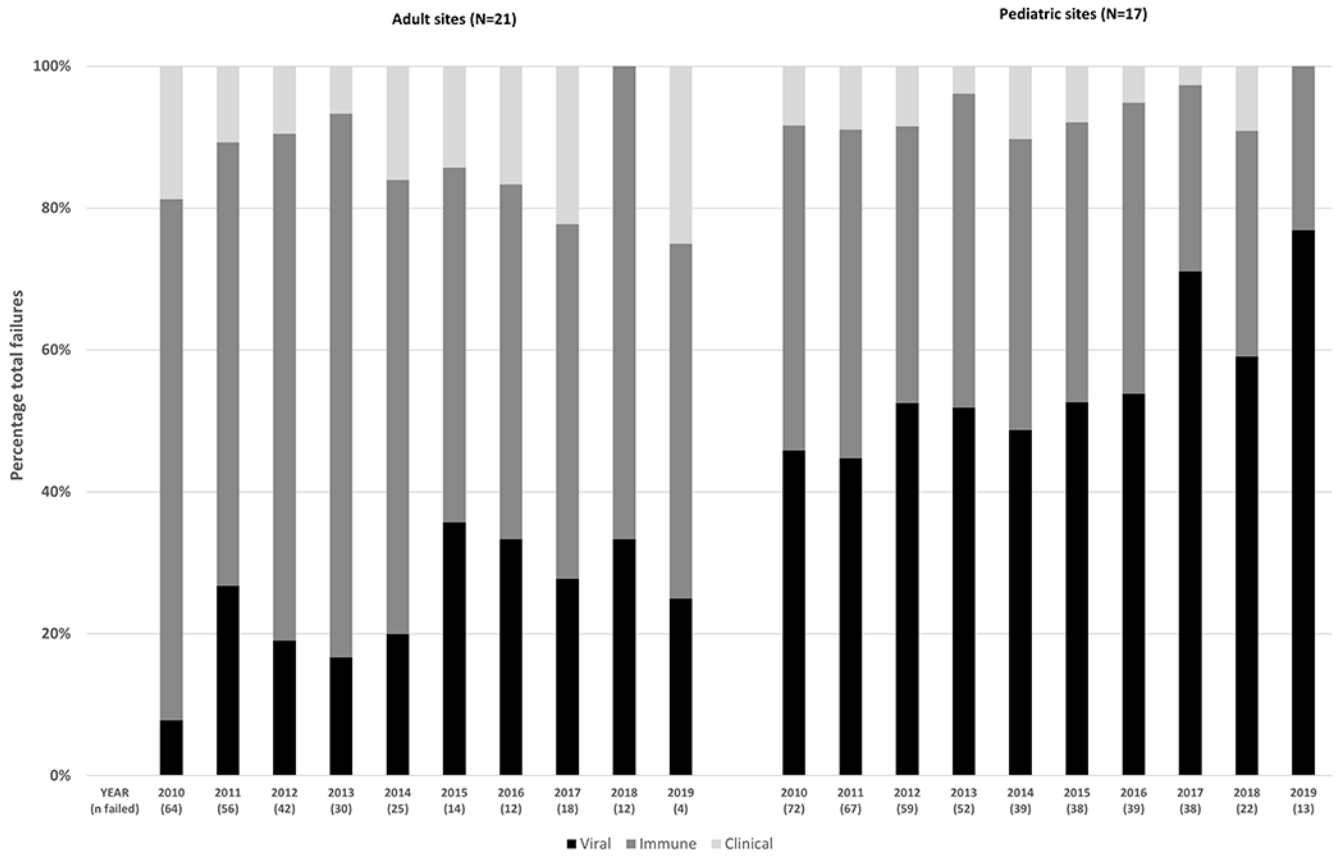


Figure 3.
Calendar year trends in the type of antiretroviral therapy failure

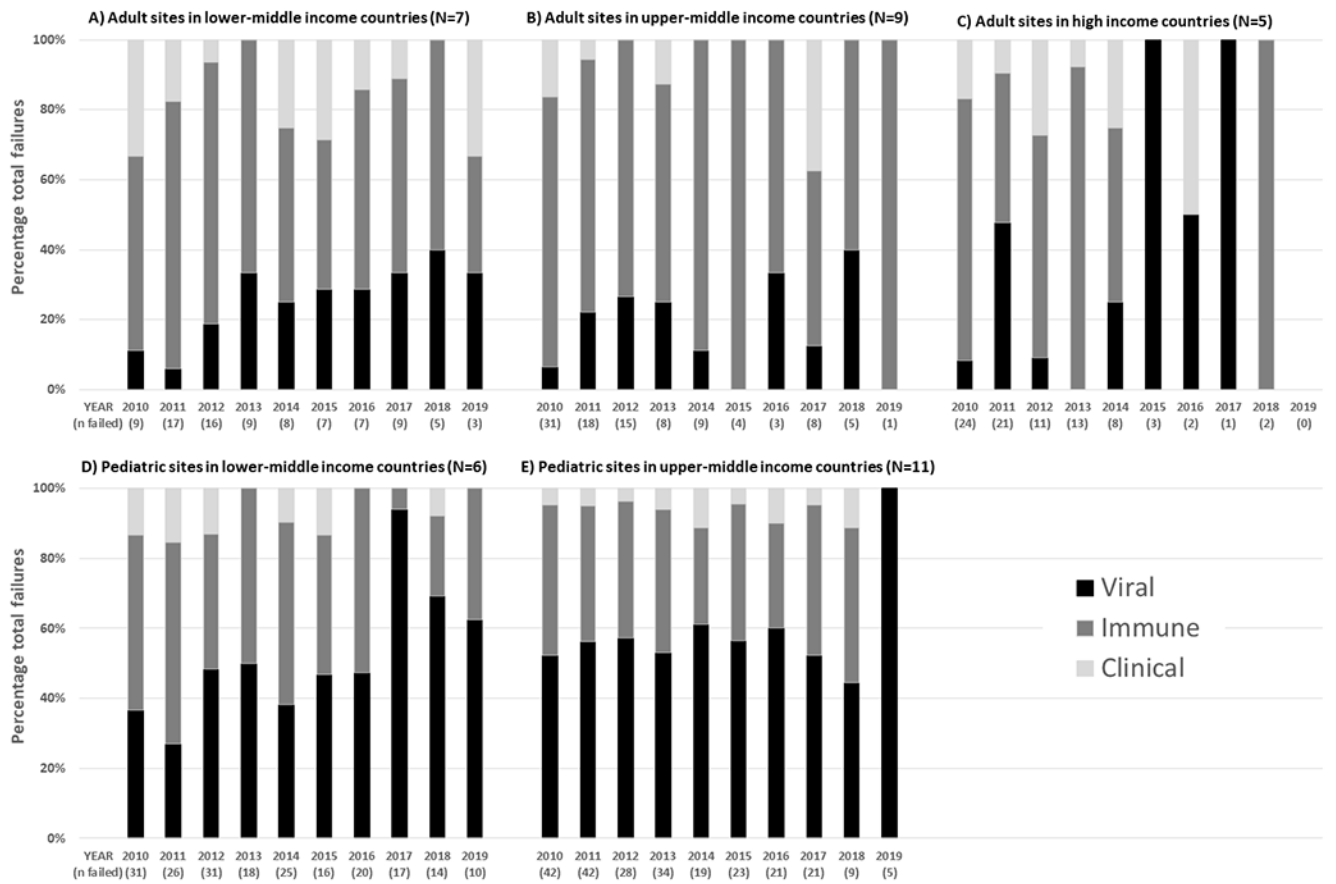


Figure 4.
Calendar year trends in the type of antiretroviral therapy failure by country income status

Table 1.

Site characteristics (Adult N=21, Pediatric N=17)

| Characteristic | | Adult n (%N) | Pediatric n (%N) |
|-------------------------|--------------|--------------|------------------|
| Country income status * | Lower-middle | 7 (33.3) | 6 (35.3) |
| | Upper-middle | 9 (42.9) | 11 (64.7) |
| | High | 5 (23.8) | 0 (0.0) |
| Public/Private | Public | 18 (85.7) | 16 (94.1) |
| | Private | 3 (14.3) | 1 (5.9) |
| Academic affiliation | Yes | 17 (81.0) | 17 (100.0) |
| | No | 4 (19.0) | 0 (0.0) |
| Patient load | <1,000 | 5 (23.8) | 14 (82.4) |
| | 1,000-5,000 | 9 (42.9) | 3 (17.6) |
| | >5,000 | 7 (33.3) | 0 (0.0) |
| Country | Cambodia | 1 (4.8) | 1 (5.9) |
| | China | 1 (4.8) | 0 (0.0) |
| | Hong Kong | 1 (4.8) | 0 (0.0) |
| | India | 3 (14.3) | 2 (11.8) |
| | Indonesia | 2 (9.5) | 2 (11.8) |
| | Japan | 1 (4.8) | 0 (0.0) |
| | Malaysia | 2 (9.5) | 4 (23.5) |
| | Philippines | 1 (4.8) | 0 (0.0) |
| | Singapore | 1 (4.8) | 0 (0.0) |
| | South Korea | 1 (4.8) | 0 (0.0) |
| | Taiwan | 1 (4.8) | 0 (0.0) |
| | Thailand | 4 (19.0) | 5 (29.4) |
| Vietnam | 2 (9.5) | 3 (17.6) | |

* As defined in 2020 by The World Bank²⁴