

HIV drug resistance



KEY POINTS

- As 'Treat All' is rolled-out worldwide, the emergence of drug-resistant HIV has the potential to become a major public health threat, as it limits treatment options for people living with HIV.
- Global prevalence of HIV drug resistance (HIVDR) is rising, mainly due to resistance to non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs – which make up the backbone of World Health Organization (WHO) first-line antiretroviral treatment regimes.
- 2018 WHO interim antiretroviral treatment guidelines now recommend dolutegravir-containing regimes as the preferred first-line treatment because of effectiveness and its high barrier to resistance.
- Weak health systems and low levels of adherence drive HIVDR – particularly in low- and middle-income countries.
- Increasing access to viral load testing, and monitoring of other clinical factors relating to patient care, patient behaviour, and clinic and programme management can mitigate the rise of HIVDR.

Explore this page to find out more about [what drug resistance is](#), [how it affects treatment options](#), [drug resistance as a public health threat](#), [the prevalence of HIVDR](#), [responding to HIVDR](#), and [what the future holds](#).

Antiretroviral treatment (ART) is one of the most effective tools in our arsenal of interventions to fight HIV – keeping people healthy and reducing the risk of onward transmission.

But as countries roll-out the latest 2017 World Health Organization (WHO) treatment guidelines that call for all people living with HIV to be on treatment¹ HIV drug resistance (HIVDR) has the potential to become a significant barrier to reaching the UNAIDS Fast-Track goal of ending AIDS by 2030.

HIVDR is a serious emerging threat to the global scale-up of HIV treatment access – particularly in sub-Saharan Africa and other low- and middle-income countries where weak health systems and poor access to monitoring and diagnostics make managing HIV more challenging.^{2 3}

The emergence of HIVDR has occurred due to multiple factors, including stock-outs of drugs, poor health service quality and treatment interruptions. It limits HIV treatment options, increases treatment programme costs, and if left untreated, resistant virus can increase in the body to the extent that it can be transmitted.⁴

What is HIV drug resistance?

HIV drug resistance occurs when the virus starts to make changes (mutations) to its genetic make-up (RNA) that are resistant to certain HIV drugs, or classes of HIV drugs. This can happen either as a result of a prolonged period of time on treatment, or more commonly, as a result of suboptimal treatment adherence. These new mutations make copies of themselves, gradually increasing the level of the virus (viral load) in the person living with HIV – meaning treatment may no longer be effective.⁵

Understanding viral mutations

When HIV first enters the body, it will actively go about replicating. But retroviruses such as HIV have a high mutation rate, so every now and then, the virus will reproduce a copy with errors.⁶

‘Wild type’ viruses – the naturally-occurring, non-mutated forms of the virus – are most susceptible to ART, but mutated forms of the virus may be less so. When antiretroviral treatment is given in inadequate levels, we are allowing for these drug resistant mutations to be selected out and multiplied to the point that drug resistant virus becomes the primary population in the viral pool.

Depending on the specific mutation, it is possible for people to become resistant to a drug they have never taken – this is called ‘cross-resistance’.⁷ This is because some mutations affect the efficacy of different drugs within the same drug class.

Even when taking ART optimally, small populations of virus still replicate. Over time, due to mutations, the population of viruses in an individual may contain fewer viral strains susceptible to HIV treatment, and more strains that are drug resistant.⁸ This is when viral load may become higher and detectable – and the prescribing healthcare provider would consider switching out a different drug or drug class.

How does HIVDR affect treatment options?

The aim of ART is to limit HIV replication in the body, and different drug classes target different parts of this process – [the HIV lifecycle](#) – to stop HIV replicating and infecting all cells.

A viral mutation can occur at any stage of this process. For example, it may present along the reverse transcriptase enzyme, meaning the efficacy of certain drugs or drug classes can be undermined – in

this example, nucleoside/nucleotide reverse transcriptase inhibitors (NRTI/NtRTI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) drug classes.

The impact on treatment options for the patient depends on which viral mutations they have. For some drugs, such as the NRTI lamivudine and all NNRTIs, just one mutation – notably the M184V or K103N mutations – can result in high-level drug resistance.⁹ This is clinically relevant, as NNRTIs including efavirenz and nevirapine have for many years made up the backbone of first-line treatment in low-resource settings.¹⁰

As such, the global burden of HIVDR is largely the result of NNRTI resistance. For other NRTIs and most protease inhibitors (PI), high-level drug resistance requires multiple mutations to occur simultaneously. Newer ARVs and drug classes, such as the integrase inhibitor, dolutegravir, have much higher genetic barriers to resistance.

Resistance to integrase inhibitors is very rare and has only been reported in treatment-experienced individuals. No clinical trial has so far reported resistance to bictegravir or dolutegravir when these drugs are used as part of someone's initial triple therapy.¹¹

Dolutegravir had previously been expensive and out of reach in low-resource contexts, but this is no longer true. Generic fixed-dose combination of tenofovir disoproxil fumarate, lamivudine, and dolutegravir (TLD) is now available at prices comparable to current regimes in most low- and middle-income countries.¹²

New 2018 interim WHO guidelines now also call for countries to move to TLD as the preferred first-line regime for all people starting treatment.¹³

There are hundreds of viral mutations associated with antiretroviral resistance. [The Stanford HIV Drug Resistance Database](#) keeps an up-to-date record that helps clinicians and programmers to interpret results from drug resistance tests.

Testing for HIV drug resistance

There are three main tests used to detect HIVDR in an individual – these are genotypic, phenotypic and viral load tests. Individual-level HIVDR testing is not widely available in low- and middle-income countries.

Genotypic and phenotypic tests are expensive, require significant laboratory infrastructure, take several weeks to process, and produce results which are complex to interpret. They are therefore not generally recommended by WHO for use for first- or second-line treatment selection in LMICs – except in countries where pre-treatment drug resistance has exceeded 10%. Yet still, only a handful of countries in sub-Saharan Africa have WHO-accredited HIV genotyping laboratories.¹⁴

But these tests are standard in high-income countries for people just starting ART, and for those experiencing virological failure (when ART fails to suppress viral load), as a means to select the optimum combination of drugs for treatment success.

Genotypic resistance testing

Genotype tests look at the specific genetic sequence within the viral DNA to assess whether there has been any change in structure compared to a 'wild type' virus (a viral sample with no genetic

mutations or drug resistance). This type of test will detect specific mutations within the genetic structure of the virus.

In high-income countries, all treatment-naïve people receive this test before starting treatment to give clinicians a better idea of what treatment regime to use.¹⁵ In lower income countries, where national levels of HIVDR are greater than 10%, and non-NNRTI regimens are not first-line, then genotypic testing can be used to guide ART selection.¹⁶

Phenotypic resistance testing

Phenotype tests look at the impact of mutations on resistance in practice. They test the dose of antiretroviral drugs needed in order for viral replication to stop (testing each drug separately).¹⁷ These tests are generally conducted on treatment-experienced patients who have failed a drug regime in high-income countries.

Viral load testing

Viral load testing is another tool which the WHO supports to monitor viral load and identify potential drug resistance, particularly where genotypic and phenotypic testing are not routinely available.¹⁸

Viral load tests look at the amount of virus in the body and are a major indicator of HIV treatment success or failure. Regular viral load testing can detect failing treatment early and before too many viral mutations occur, meaning changes in therapy can be minimal and less costly. However, access to even this type of treatment monitoring tool is inadequate in low- and middle-income countries.

HIVDR as a threat to public health

What drives HIV drug resistance?

HIV drug resistance can arise from a range of different factors, which can be split up into four broad categories – patient, programming, drug regime and virus-specific drivers of drug resistance.^{19 20}

Patient factors

A number of individual-led reasons may stop a person taking their drugs as prescribed, increasing their risk of developing drug resistant mutations.

This could be the result of a lack of understanding of HIV, treatment and the implications of stopping their medication, having to take a lot of pills and frequently, being forgetful, and depression, substance or alcohol abuse.²¹ These are issues that affect adolescents in particular, because they may find it hard to prioritise their health over social engagements. Children also face unique challenges because they have less treatment options available to them and rely on others to manage their health.

Stigma and disclosure of HIV status to others may also present a challenge for people trying to keep a regular drug-taking regime.²²

Programme factors

Programme-specific drivers of HIVDR refer to challenges arising from the delivery of large-scale or

country-level HIV treatment programmes which in turn affect an individual's ability to stick to a treatment regime.²³

Drug stock-outs, where people cannot get their drugs because the pharmacy doesn't have their treatment, is also a programmatic driver of HIVDR.²⁴ Poor drug procurement and supply chain management are largely to blame, in addition to poorly resourced human capital and infrastructure.²⁵ In these settings, regular viral load testing is also limited, meaning healthcare providers cannot properly monitor for the emergence of HIVDR.

Poorly resourced treatment programmes may also be the result of weak monitoring and evaluation of care outcomes, and also from decentralised service delivery.

Drug and treatment regime factors

Regime and drug-specific factors refer to the selection of specific antiretroviral regimes that may increase or decrease the likelihood of HIVDR, with different types of drugs and drug classes having varying genetic barriers to resistance

NNRTI-based treatment regimens are still commonly prescribed as first-line treatment, and while these drugs are effective, they are more susceptible to drug resistance over other treatment regimens – such as boosted PI-based or integrase-based regimes.²⁶ Providing treatment in one single-pill fixed-dose means people are more likely to adhere to their drug taking regime; it also makes it easier for drug procurement.

Sub-optimal prescribing of ARVs, such as single tablet nevirapine or zidovudine for pregnant women, as well as use of just one of two types of drug for HIV therapy also increase the risk of HIVDR as they allow for mutations to occur in the presence of drugs already in the body.²⁷

Viral factors

Virus-related factors refer to resistance that arises by nature of the HIV type or subtype that may affect a drug regime. For example, HIV-2 is intrinsically resistant to NNRTIs, so people with this strain of HIV should not have NNRTIs included in their regime.²⁸ Also, some evidence suggests that thymidine analog mutations – caused by the drugs zidovudine and stavudine – may develop more quickly in people with HIV subtype C.²⁹ These cannot be helped on their own, but if the healthcare provider is aware, they can control the progressions of drug resistance by addressing other drivers.

Types of HIVDR

The WHO has identified three types of HIV drug resistance that threaten to derail the HIV response.³⁰

- Transmitted HIVDR (TDR) – occurs when an uninfected, treatment-naïve person is infected with a drug-resistant strain of HIV from someone with HIVDR mutations.
- Acquired HIVDR (ADR) – occurs when a treatment-experienced person living with HIV develops drug mutations in the presence of ART as a result of sub-optimal treatment adherence, treatment interruptions, inadequate drug concentrations in the body, or the use of suboptimal drugs and combinations.
- Pre-treatment HIVDR (PDR) – HIVDR that is detected at the time of first-line ART initiation or re-initiation, that could be due to transmitted drug resistance, or HIVDR acquired as a result of previous ARV exposure, such as mothers and children in prevention of mother-to-child

transmission programmes (PMTCT).[31](#)

HIVDR in children

The impact of drug resistance on treatment outcomes in children and adolescents is a growing concern, particularly in sub-Saharan Africa where the majority of children living with HIV reside.[32](#) In general, treatment options for children are limited, as it is more difficult to develop paediatric drugs than it is for adults.[33](#) Second-line treatment options for children are therefore costly, meaning access to these drugs in low-resource settings can be a challenge.[34](#)

In addition to this, virological outcomes for children are generally poorer compared to adults, as they face unique treatment barriers.[35](#) [36](#) Paediatric drug formulations and pharmacokinetics can result in suboptimal drug levels allowing for the selection of resistant mutations – particularly as children grow and their body weight changes.[37](#)

Children also face unique challenges relating to treatment adherence.[38](#) These challenges could relate to the medication itself, for example, they may not like the taste of the medicines, or they may have to take multiple pills, making sticking to a drug-taking regime difficult. Other challenges relate to the fact that children depend entirely on the caregiver to ensure that they are taking their medication consistently, who may themselves have their own adherence challenges.[39](#)

HIVDR and PrEP

While taking PrEP is not directly linked to the emergence of HIVDR, regular testing for HIV while on PrEP is important to ensure that people aren't inadvertently taking suboptimal HIV treatment should they become HIV-positive while on PrEP.[40](#)

For most PrEP programmes, people are engaged in care, receiving the support and HIV testing they need to stay healthy. But as more people access PrEP directly through the internet, or through non-healthcare channels, there is the risk that they may not be adhering to the treatment as they should and may not go for regular testing. They are therefore at risk of being HIV positive and continuing to take PrEP, rather than transitioning to a treatment programme. It is important that PrEP is delivered with adequate information and support so that its positive effect can be maximised.

Modelling studies have shown us that concerns over the emergence of PrEP-related drug resistance should not be a reason to limit PrEP access. One such study showed us that over 20 years of ART and PrEP scale-up in sub-Saharan Africa, just 4% of HIVDR would be attributed to PrEP, compared to 50-63% for ART, and 40-50% for transmitted drug resistance.[41](#)

While the results from modelling studies are positive, large-scale PrEP programmes will still require active monitoring of HIVDR to ensure their efficacy in the long-run.[42](#)

Global prevalence of HIVDR

The numbers of people with drug resistant virus has increased over time, and as previously highlighted, is largely the result of growing levels of resistance to NNRTI drugs in sub-Saharan Africa.[43](#) One reason for this is that just one mutation – notably the K103N mutation – causes high-level resistance to the NNRTIs efavirenz and nevirapine and cross-resistance between the two drugs. This leaves few treatment options for drugs in this class[44](#)

To put this into perspective, in 2016, efavirenz and nevirapine were used in 86% and 14% of adults, and 29% and 47% of children on first-line HIV treatment.⁴⁵

In 2012, the WHO noted that pre-treatment drug resistance had reached 9% globally – rising from 6.9% in 2010.⁴⁶ In their latest available data, the WHO predicted that pre-treatment resistance to NNRTIs had reached 15.5% in East Africa, 15% in Latin America, 11% in Southern Africa and 7.2% in West and Central Africa in 2016.⁴⁷ They also reported the estimated incremental annual increase of NNRTI resistance to be 29% in eastern Africa, 23% in Southern Africa, 17% in West and Central Africa, 15% in Latin America and 11% in Asia.⁴⁸

In 2017, six out of 11 low- and middle-income countries implementing national drug resistance surveys reported pre-treatment drug resistance above 10% – Argentina, Guatemala, Namibia, Nicaragua, Uganda and Zimbabwe. In Africa, NNRTI resistance ranged from 8.1% in Cameroon, to 15.4% in Uganda. In Latin America, HIVDR prevalence of any drug class ranged from 9.8% in Brazil, to 23.4% in Nicaragua.⁴⁹

Other studies have also reported high levels of pre-treatment drug resistance in several countries – up to 16% in Angola, 13% in Argentina, 10% in Botswana, 22% in Cuba, 15% in Mexico, 16% in Papua New Guinea and 14% in South Africa.⁵⁰ Levels of pre-treatment drug resistance were twice as high among people re-initiating ART – either because they had previously been exposed through PMTCT or because they had stopped their treatment – than those who are completely ART-naïve.^{51 52}

HIVDR in the context of PMTCT scale-up

The mass scale-up of prevention of mother-to-child transmission services, from Option B to Option B+ is the major success story of the HIV response, but as less children are born with HIV, there is the risk that drug resistance will increase in the fewer children that do become HIV-positive.⁵³ The WHO estimates that one out of two children newly diagnosed with HIV has a virus resistant to either efavirenz or nevirapine.⁵⁴

In a study of 2,617 children across 13 low- and middle-income countries, they found pre-treatment drug resistance to be high, and increasing rapidly among African children.⁵⁵ Pooled PDR prevalence was 42.7% among PMTCT-exposed children and 12.7% among PMTCT-unexposed children. In unexposed children, this had increased by over a quarter (26.8%) between 2004 and 2013.⁵⁶

The increase in drug resistance among children with no previous exposure to PMTCT, underscores the possibility of high levels of transmitted drug resistance in mothers failing their ART regimes and passing on a mutated virus to their children.^{57 58} From 2013, the WHO has recommended protease-based regimes using lopinavir for all children under three starting treatment, irrespective of exposure to PMTCT. But NNRTIs are still widely used across sub-Saharan Africa, which affect treatment outcomes for children.

The increase in HIVDR among infants and children is alarming. In a Togo national PMTCT programme, 60% of a cohort of newly diagnosed children had detectable relevant drug resistant mutations – with high levels (81.8%) of NNRTI resistance detected.⁵⁹

HIVDR among Zambian infants nearly doubled between 2007/2009 and 2014 – from 21.5% to 40.2%. NNRTI resistance increased steadily over this period, while NRTI resistance increased three-fold, with strength of resistance increasing over time and in the era of PMTCT scale-up.⁶⁰

In a South African survey submitted to the WHO, 63.7% of children living with HIV under 18 months had some form of HIVDR.[61](#)

Future impact of HIVDR

Modelling studies have been conducted to understand what could be the projected impact of drug resistance in the next 15 years to 2030. These assume no change in regimes, nor any introduction to baseline drug resistance testing. In sub-Saharan Africa, if the level of PDR is around 10% or more, the number of AIDS deaths attributed to HIVDR in the next 15 years could be around 890,000 – around 16% of total AIDS deaths. We could see 450,000 new HIV infections – 9% of all new HIV infections. ART could cost an extra \$6.5 billion – around 8% of total ART needs to 2030.[62](#)

Even when PDR remains low, at below 10%, the projected impact on the epidemic is still large – with 710,000 AIDS deaths, 380,000 new infections and \$5.0 billion in extra ART costs by 2030.[63](#)

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Responding to HIVDR

In July 2017, the WHO released three major reports to respond to HIV drug resistance - including new treatment guidelines, a Global Action Plan, and a global report on HIVDR - the first since 2012.

The five-year [Global Action Plan](#) – centred on five key objectives – aims to support countries to prevent HIVDR through interventions to strengthen treatment programmes, effective monitoring, research and innovation, increasing laboratory capacity, and ensuring country ownership on this issue.

2017 and 2018 WHO treatment guidance

In 2017, the WHO recommended that a public health response be triggered in countries where pre-treatment HIVDR exceeded 10% - meaning countries should consider alternative, non-NNRTI treatment regimens for individuals starting ART using dolutegravir.

In July 2018, however, new interim guidelines were released recommending that all adults living with

HIV and starting treatment should start using dolutegravir-based regimes. This is because of the increased effectiveness of these regimes, their high barriers to resistance, but also because they are now more easily accessible in generic form.

HIVDR surveillance

In 2004, the WHO developed an HIVDR surveillance strategy to help countries monitor HIVDR and provide them with actionable data.⁶⁴ The strategy included the surveillance of pre-treatment HIVDR in all adults starting first-line treatment; the surveillance of acquired HIVDR in adults and children on treatment; and the surveillance of HIVDR in infants less than 18 months.⁶⁵ Later updated in 2015, the strategy also includes the monitoring of a set of 'Early Warning Indicators' (EWIs) for drug resistance at all ART clinics.⁶⁶

Early Warning Indicators (EWIs) for HIVDR

Countries with limited resources for monitoring the emergence of drug resistance can track HIVDR through the monitoring of WHO's 'Early Warning Indicators' (EWIs) for drug resistance. These EWIs help countries to identify vulnerabilities in HIV treatment programmes that could potentially lead to HIVDR using simple clinical information – such as factors relating to patient care, patient behaviour, and clinic and programme management.

Any gaps in treatment or service delivery can be identified in a timely manner, which can then inform policy changes, public health actions, or programmatic changes to then minimise the emergence of HIVDR.

The annual monitoring of EWIs provides a relatively easy and inexpensive means for monitoring factors related to the emergence of HIVDR in limited-resource settings and should be integrated into national HIV programmes.⁶⁷ Specifically, the EWI's include:

- Treatment regimens are prescribed optimally and according to national or international guidelines – described as the percentage of all ART prescriptions that are consistent with guidelines. That is, ensuring people have moved away from mono- or dual-therapy regimes in favour of highly active antiretroviral therapy consisting of three drugs. Or, where toxic or ineffective drugs have been phased out, the percentage of people who have moved away from these regimes.
- Loss to follow-up (LTFU) after 12 months – measured as the percentage of people with unknown clinical outcomes one year after starting treatment. Patients are recorded as still being at the clinic and in treatment, transferred out of the clinic, still at the clinic but stopped treatment, died, or LTFU. Many of these patients who are LTFU may be 'silent transfers', i.e. patients who have been picked up by another clinic for treatment. While little is known about silent transfers, it is highly likely that they experience treatment interruptions and are at a higher risk of HIVDR. A clinic should therefore aim for minimal LTFU after treatment initiation.
- Retention on ART at 12 months – patients who do not remain on ART and experience treatment interruptions are at the biggest risk of developing drug resistant virus. Measuring those who have remained on treatment after 12 months is critical, particularly as in sub-Saharan Africa, mortality is highest in the first two years after people start treatment. Identifying those patients who have disengaged with care or have been LTFU will pave the way for the development of strategies to minimise the impact of this on public health.⁶⁸
- On-time pill pick up/ on-time clinic appointment keeping – treatment non-adherence of just 48

hours has been linked to the development of drug resistant HIV mutations. While it is difficult to monitor patient adherence to ART, certain proxies can be used to determine if a patient is taking their medicines – such as those picking up their treatment on time, and keeping appointments at the clinic. These measure successful engagement of patients in care.

- Drug stock-outs – country procurement of antiretroviral drugs as well as supply chain management are essential components of the delivery of large scale ART programmes – because stock-outs are linked to treatment non-adherence. This data relates to a pharmacy's ability to maintain a continuous routine supply of key drugs that are most used in the area.
- Viral load monitoring and viral load suppression – measuring viral load is one of the strongest tools we have to indicate treatment success and the onset of drug resistance. Ensuring patients have regular access to viral load monitoring – measured as the percentage of patients having at least one 12 month viral load test – as well as the percentage of patients who are considered virally suppressed after 12 months, will mitigate HIVDR.

What do the EWIs tell us?

A [global WHO report on the EWIs released](#) in 2016 revealed significant variations in the quality of treatment programming across and within countries. Overall, more attention is needed to decrease levels of loss to follow-up, support retention, improve adherence and prevent drug stock-outs.

The most recently available data compiled from 59 countries and more than 12,000 clinics from cohorts of patients receiving ART between 2004 and 2014 showed that globally, 20% of patients went missing one year after starting treatment – reaching close to 30% in West and Central Africa. Just 74% of all patients globally remained on ART after 12 months – falling short of the WHO goal of 85%. Again, West and Central Africa lagged behind at 64% and 59% respectively. Delays in drug pick-up and lack of appointment keeping were also worryingly low, but limited data meant that regional trends could not be extracted. Notably, at least 36% of clinics had at least one drug stock-out of routinely dispensed ARVs in a reporting year.⁶⁹

Through the monitoring of the EWIs, countries have been able to make changes to their treatment programmes – improving treatment programme efficiencies and health outcomes. But these national data are more for understanding trends at the global level. The EWIs also play an important role in understanding variability in clinic performance within countries, which can help decision makers focus resources on the clinics that are most in need.

Clinic-level determinants of retention could include clinic location, whether it is urban or rural; the size of the clinic; whether services are centralised vs. decentralised, or whether task-shifting is used.

HIVDR - what needs to happen now?

What is clear is that concerns over the rising prevalence and potential impact of HIV drug resistance should not stop global treatment expansion.

Critical to the success of 'Treat All' and reaching the Fast-Track targets by 2030, is the delivery of successful HIV programmes where every person living with HIV is aware of their status, receiving the treatment they need, and adhering to it as prescribed.

Nevertheless, the benefits of universal treatment access cannot be experienced without the appropriate tools for monitoring treatment failure and making appropriate changes where needed.

While HIVDR has major consequences for low- and middle-income countries which face challenges in HIV treatment delivery, the monitoring of the WHO EWIs will help these countries optimise HIV treatment and care programmes to prevent HIVDR – by pinpointing clinics and areas that may be falling behind. Since 2011 however, the monitoring of EWIs by countries has fallen markedly.⁷⁰

Innovative solutions and technologies to better monitor for drug resistance are needed, beyond the clinical drivers that we can monitor via the EWIs. These must be ones that are affordable, at point-of-care, and in the places they are needed most.

Countries also need to ensure they are procuring drugs that are affordable – seeking innovative partnerships to get the drugs on the ground, to those who need them – aided by efficient supply chain management and infrastructure development.

The potential impact of HIVDR can be avoided through the strengthening of health systems and increased access to viral load monitoring in low-resourced settings, with population level treatment adherence critical to ending AIDS by 2030.

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