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STUDY REVIEW

GEMINI-1 and GEMINI-2

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About the Expert

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Professor Boyd is an internationally recognised infectious disease expert. He has led project teams in HIV research in Thailand, as well as at the Kirby Institute for infection and immunity at the University of New South Wales. He played a key role in two major, multicentre, international randomised clinical trials ('SECOND-LINE' and 'Encore1') sponsored by the Kirby Institute, which have brought changes to the WHO guidelines on the antiretroviral management of HIV infection in adults and adolescents.

Until mid-2016 Professor Boyd was an Associate Professor at the Kirby Institute, a consultant physician in HIV Medicine and Infectious Diseases and a Visiting Medical Officer in inner Sydney as well as regional NSW. Mark is the founding Chair of Medicine at the University of Adelaide based at the Lyell McEwin Hospital in South Australia.

He has published more than 130 papers, book chapters, reviews and commentaries and been an investigator on grants worth in excess of 21 million AUD.

In 2014 he was awarded the Frank Fenner Award for Advanced Research in Infectious Diseases by the Australasian Society for Infectious Diseases for clinical research that has changed WHO guidelines for the use of first- and second-line antiretroviral therapy worldwide. In 2018 he was invited to join the WHO Clinical Antiretroviral Guidelines Development group and in 2019 the WHO HIVResNet Research and Innovation Working Group.

Abbreviations used in this review:
2DR = two-drug regimen
3DR = three-drug regimen
ART = antiretroviral therapy
ARV = antiretroviral
ATV/r = atazanavir/ritonavir
DDI = drug-drug interactions
DTG = dolutegravir
EFV = efavirenz
DRV/r = darunavir/ritonavir
FTC = emtricitabine
INI = integrase inhibitor
LPV/r = lopinavir/ritonavir
PLHIV = people living with HIV
RAL = raltegravir
TAF = tenofovir alafenamide
TDF = tenofovir disoproxil fumarate
WT = wild-type

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Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naïve adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials.[1]

Introduction

Combination antiretroviral therapy (ART) containing three active drugs from at least two different classes has been the standard of care for HIV since 1996.[2,3] Although available three-drug regimens (3DR) are potent, convenient, and generally well tolerated, issues of toxicity, potential multiple drug interactions and cost remain over decades of exposure. A virologically potent two-drug regimen (2DR), with the potential to reduce toxicity and improve tolerability, could address these issues and become the new standard-of-care.

Now that we have more potent drugs, the focus is shifting to tolerability and convenience and the potential for a decrease in drug–drug interactions (DDIs). Having fewer agents in the ART regimen means fewer agents to interact, while improvements in pharmacokinetics and efficacy of newer agents means a decrease in dosing frequency.

Why consider a two-drug regimen?

Potential benefits of reducing antiretroviral (ARV) drug exposure by utilising a 2DR are several-fold. These include reduced toxicities,[4-11] reduced long-term care/societal costs,[12,13] improvements in access,[13] improvements in patient satisfaction e.g. reduced dose adjustments and DDIs,[14] and preservation of drug effect for ARVs not included in the regimen (Figure 1).

Life expectancy among people living with HIV (PLHIV) is approaching normal;[15] a 20-year-old starting ART in 2008–2010 can now expect to live until approximately 78 years of age.[15] This means that PLHIV will be on ART for decades; the mean estimated duration of lifetime treatment in 2012 was 39.1 years.[16] Marcus et al. showed that, even with early treatment, an approximate 8-year gap in life expectancy remains for HIV-infected versus HIV-uninfected individuals.[17] The gap in life expectancy was decreased in participants without a history of hepatitis B virus or hepatitis C virus infection, substance abuse, or smoking.[17] Other factors that may contribute to the survival disparity for PLHIV include cancer,[18] cardiovascular disease,[19] and other aging-associated comorbidities.[20] Timely ART initiation and risk-reduction strategies, such as smoking cessation, are important to increase the life expectancy of PLHIV.

Furthermore, unmet needs still persist for PLHIV. A survey conducted between 2016 and 2017 involving over 1000 PLHIV from North America, Europe, and Australia found that almost three quarters of participants sometimes worried about the long-term effects of their HIV medications.[21] Reduction of long-term adverse effects and longer treatment intervals were viewed as more important potential medication improvements than reduction of short-term side effects and pill burden.

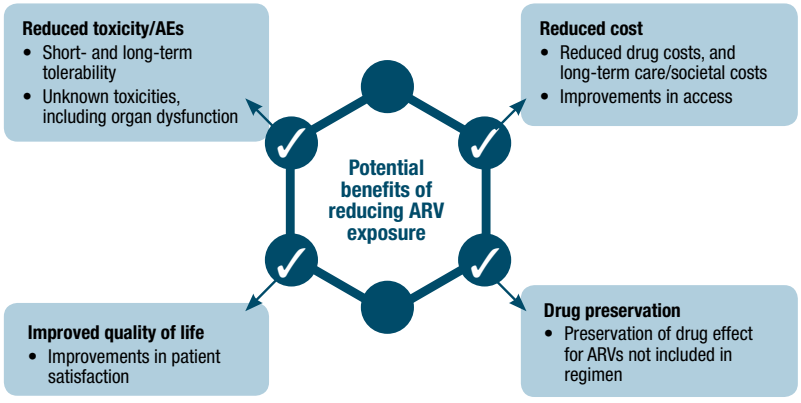

Figure 1. Benefits to reducing antiretroviral drug exposure.[4-11]

As the HIV-positive population ages, polypharmacy becomes increasingly common. Findings from a pharmacist care plan programme in Victoria, Australia, found that 85% of PLHIV aged over 50 were taking five or more medications including ART.[22] At least one drug interaction was reported by 33 (68.8%) patients and 18 (37.5%) patients had two or more.

Many widely used ARVs have subsequently shown unexpected toxicities long after their initial introduction, regardless of drug class.[4-11,23-30] It is likely that all ARVs have a risk of long-term or cumulative toxicity; therefore, it is appropriate to reduce ARV drug exposure if possible.

Assuming a mean estimated duration of lifetime treatment of 39.1 years,[16] patients treated with a non-boosted once-daily 2DR would receive only half the number of drug exposures as once-daily, boosted triple-therapy-treated patients over their lifetime.

EXPERT COMMENTARY ON CONSIDERING A TWO-DRUG REGIMEN

For the past two decades it has been considered almost incontrovertible that combination antiretroviral regimens must contain a minimum of three antiretroviral drugs.

Despite that there have been hints along the way that this may not necessarily be the case. Randomised trials such as Merck 006[31] and ACTG 5142[32] which were mainly designed to test the use of three-drug ART also contained 2DR arms. These 2DR groups did reasonably well in terms of antiretroviral efficacy but failed to gain traction due to higher rates of antiretroviral resistance at virological failure and metabolic disturbance. A systematic review and meta-analysis published by Achhra and colleagues in 2016 showed that while a 3DR was slightly favoured numerically, the difference was not statistically significant.[33] Another key consideration is that triple therapy itself is not an assurance of a sustained virological response. The ACTG 5095 study showed that the triple combination of abacavir + zidovudine + lamivudine was inferior to a triple combination of efavirenz + zidovudine + lamivudine in ART-naïve subjects.[34,35] This observation itself leads to the possibility that what is more important than the use of three drugs is that the drugs must target at least two separate processes in viral replication. That is, the while abacavir and lamivudine and zidovudine add up to three drugs they all act as 'nucleoside dummies' for the reverse transcriptase (RT) phase of intracellular HIV replication, i.e. one single target. By contrast the three-drug combination of efavirenz + zidovudine + lamivudine targets two separate mechanisms of HIV replication – nucleoside dummies (zidovudine and lamivudine) and a separate target that affects the conformity of the RT enzyme reducing the efficiency of that enzyme. When thought of from this perspective one could say that the paradigm of combination ART is not really shifted at all, i.e. both 3DR and 2DR target two independent mechanisms of viral replication.

Trials of two-drug regimens

There were some RCTs which suggested that a 2DR was feasible, but it was a matter of finding the right pairings.[32,36-38] A once-daily nucleoside-sparing 2DR of maraviroc and darunavir/ritonavir was inferior to a 3DR of tenofovir/emtricitabine and darunavir/ritonavir in antiretroviral-naive adults.[36] A 2DR comprising efavirenz plus ritonavir-boosted lopinavir was non-inferior to standard treatment of efavirenz plus two nucleoside reverse transcriptase inhibitors but was associated with increased emergence of drug resistance.[32] In a phase 3 trial, raltegravir plus ritonavir-boosted darunavir was non-inferior to a 3DR in the overall population of treatment-naive participants.[37] However, the 2DR was inferior to the 3DR in the subgroup of participants with CD4+ counts of less than 200 cells/μL and did not show non-inferiority in the subgroup of participants with baseline HIV-1 RNA of more than 100 000 copies/mL.

Dolutegravir as part of a two-drug regimen

The rationale for dolutegravir as a core agent to support 2DRs is detailed in Figure 2. Dolutegravir is an integrase strand transfer inhibitor for use in combination with other antiretroviral agents for the treatment of HIV infection. Dolutegravir is a once-daily* drug that can be taken with or without food[39] and has a low potential for DDIs.[40] There is a large body of evidence with up to 144 weeks of follow-up showing that dolutegravir as part of a 3DR has potent virological efficacy, a favourable tolerability profile, and a high barrier to resistance.[41-44]

Lamivudine is a potent nucleoside reverse transcriptase inhibitor devoid of major adverse effects, with a well-proven safety profile and a high barrier to resistance.[45-50] One of the most common treatment-emergent mutations, M184V, reduces the replicative fitness of HIV, potentially increasing susceptibility to other nucleoside reverse transcriptase inhibitors.[46-48]

Lamivudine is administered once daily with or without food and no clinically relevant DDIs have been reported with its use.[45] The GARDEL study demonstrated noninferiority of a 2DR of lopinavir/ritonavir plus lamivudine to lopinavir/ritonavir plus two nucleoside reverse transcriptase inhibitors.[51] Similarly, the ANDES trial showed that ritonavir-boosted darunavir plus lamivudine was non-inferior to a ritonavir-boosted darunavir-based 3DR.[52] These studies suggest that lamivudine is a good option for a 2DR with an antiretroviral agent with a high barrier to resistance. However, these 2DRs included ritonavir-boosted protease inhibitors, which are an unsatisfactory initial ART due to gastrointestinal and metabolic toxicity and high risk of DDIs.[53]

The 2DR of dolutegravir plus lamivudine was evaluated in 20 ART-naïve participants in the pilot PADDLE study.[54] Ninety percent of the study population had undetectable viral load at week 48, and remained suppressed at week 96.[55] Subsequently, in the ACTG A5353 study of 120 ART-naive participants with HIV-1 RNA <500 000 copies/mL, dolutegravir plus lamivudine, resulted in undetectable viral load in 90% of the study population at week 24, regardless of baseline HIV-1 RNA.[56] Dolutegravir has a different mechanism and site of action to lamivudine. This ensures that dolutegravir plus lamivudine blocks the viral life cycle at two different targets like traditional 3DRs.[28,45]

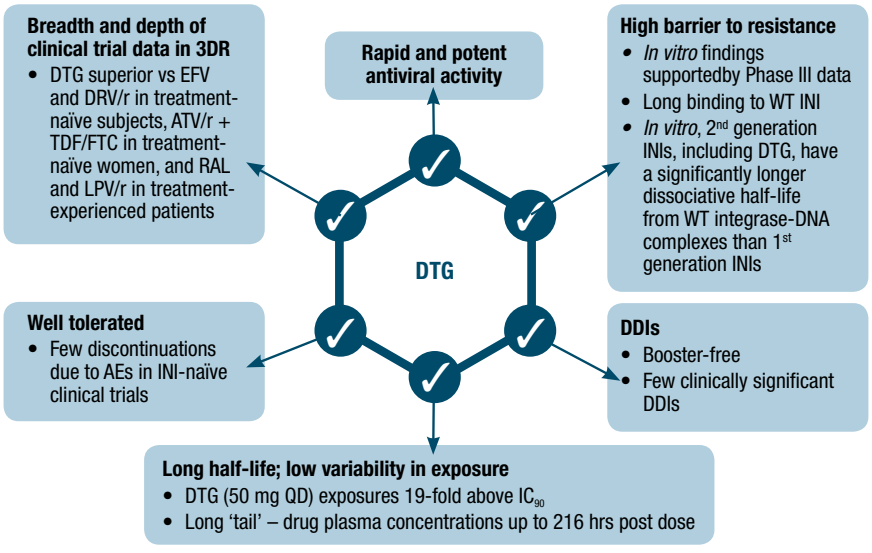

Figure 2. Dolutegravir as a core agent to support two-drug regimens.[28,57-68]

*Dolutegravir should be taken twice daily in individuals with HIV-1 with resistance to the integrase class (documented or clinically suspected)[28]

M184V resistance and the implications for lamivudine plus dolutegravir

M184V is a single mutation that confers high level resistance to lamivudine and can lead to increased viral loads.[69] Over 50% M184V is required to confer effective resistance to lamivudine.[70] However, lamivudine monotherapy may lead to a better immunological and clinical outcome than complete therapy interruption, suggesting that lamivudine maintains some functionality even in the presence of M184V.[71] M184V has a positive effect on HIV-1 reverse transcriptase fidelity, reducing spontaneous HIV mutagenesis.[72] The processivity of reverse transcriptase may be affected, with reduced viral replication versus WT viruses *in vitro* and *in vivo*.[72] M184V can increase the susceptibility of the virus to other NRTIs and delay the emergence of resistance to zidovudine, tenofovir disoproxil fumarate and possibly dolutegravir.[73,74] Some guidelines suggested continuing lamivudine despite the presence of M184V, because they offer some residual activity and M184V can reduce the virus's virological fitness.[75,76] *In vitro*, the M184V mutation antagonises emergence of dolutegravir-resistance mutations.[74] However, in the absence of drug pressure M184V has a fast rate of reversion; within two months 40% reverted to wild type, with the replicative capacity increasing by 53.5%.[73]

GEMINI-1 and GEMINI-2 trial design

GEMINI 1 and GEMINI 2 are duplicate, phase III, randomised, double-blind, multicentre, parallel group, non-inferiority studies.[1] These ongoing studies evaluate a single-tablet, 2DR of dolutegravir and lamivudine compared with a standard three-drug, first-line regimen in HIV-1 infected, ART-naïve adult participants with baseline viral loads <500,000 copies/mL. The studies are designed to demonstrate the non-inferior efficacy, safety, and tolerability of once-daily dolutegravir and lamivudine compared to the 3DR of once-daily dolutegravir and the fixed-dose combination of tenofovir disoproxil fumarate and emtricitabine (Truvada®) at 48 weeks. The primary endpoint is the proportion of patients with plasma HIV-1 RNA <50 copies/mL at week 48 using the FDA snapshot algorithm (missing, switch or discontinuation = failure). The non-inferiority margin is –10%.

EXPERT COMMENTARY ON TRIAL DESIGN

The identical GEMINI 1 and 2 trials are examples of the high standard trials required for licensing of new ART products around the world. By comparing the 2DR with a conventional standard of care 3DR in a double-blinded fashion one can be assured that the findings are robust and reliable and should contribute to a recommendation regarding 2DR clinical use at the highest evidence level of '1' (i.e. evidence derived from at least 1 RCT with proper randomisation). The non-inferiority-margin of 10% is the current margin recommended by the US FDA for non-inferiority studies (i.e. meaning that if successful it can be stated that the experimental regimen (in this example 2DR) is no greater than 10% worse than the comparator regimen (in this case 3DR) in efficacy. The study was performed in multiple sites around the world in both high-income and middle-income countries and the results are therefore widely generalisable.

Primary endpoint

Between July 18, 2016, and March 31, 2017, 1441 participants across both studies were randomly assigned to receive either the 2DR (n=719) or the 3DR (n=722). Key demographic and baseline clinical characteristics were well balanced between the treatment groups. At week 48 in the GEMINI-1 intention-to-treat-exposed population, 320 (90%) of 356 participants receiving the 2DR and 332 (93%) of 358 receiving the 3DR achieved plasma HIV-1 RNA of <50 copies/mL (adjusted treatment difference –2.6%, 95% CI –6.7 to 1.5); in GEMINI-2, 335 (93%) of 360 participants in the 2DR group and 337 (94%) of 359 participants in the 3DR group achieved HIV-1 RNA of <50 copies/mL (adjusted treatment difference –0.7%, 95% CI –4.3 to 2.9), showing non-inferiority at a –10% margin in both studies. For the pooled analysis the primary endpoint was achieved by 91% of participants in the 2DR group versus 93% of participants in the 3DR group; the adjusted treatment difference was –1.7% (95% CI –4.4 to 1.1) (Figure 3). Virological non-response (defined by Snapshot analysis as ≥50 copies/mL at week 48) was observed in 3% of participants in the 2DR group versus 2% of participants in the 3DR group.

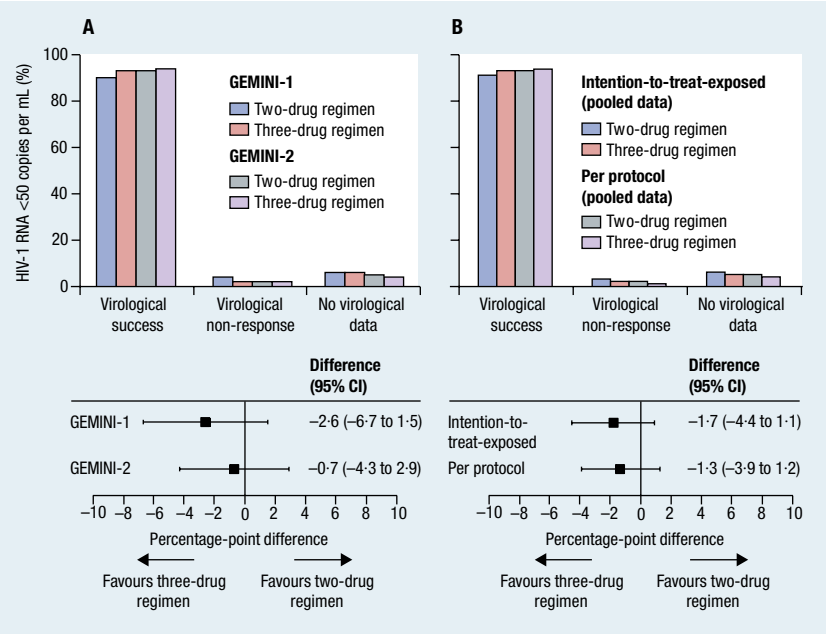

Figure 3. Snapshot analysis of participants with HIV-1 RNA <50 copies/mL at week 48.[1]

(A) Intention-to-treat-exposed populations of the separate GEMINI-1 and GEMINI-2 studies.

(B) Pooled analysis of the intention-to-treat-exposed and per-protocol populations. Treatment differences (bottom of panel) were adjusted on the basis of the Cochran–Mantel–Haenszel stratified analysis, adjusting for baseline plasma HIV-1 RNA (≤100 000 *vs* >100 000 copies/mL) and CD4+ cell count (≤200 *vs* >200 cells/μL). Non-inferiority margin was –10%. Error bars are 95% CIs.

EXPERT COMMENTARY ON PRIMARY ENDPOINT

It is important to understand that in pivotal studies such as the GEMINI-1 and GEMINI-2 studies, the primary endpoint is assessed in the 'intention-to-treat-exposed population'. This means that the population included in the primary analysis was defined as all participants who were randomised and took at least one dose of the study medication. This is the strictest form of analysis.

As can be seen in Figure 3, the 2DR performed very similarly to the 3DR with >90% of patients achieving a viral load <50 copies/mL after 48 weeks of study medication. Importantly (and as can be seen in the 'Forest Plot' beneath the bar graphs in Figure 3) the experimental 2DR satisfied the criteria for 'non-inferiority' against 3DR (i.e. the confidence intervals (or 'whiskers') around the point estimate (the black box) cross the 0 point of no-difference, indicating no statistical difference between the regimens. The per-protocol population was defined in the GEMINI studies as all participants in the intention-to-treat-exposed population except for those individuals with a protocol violation which could affect the assessment of antiviral activity.

Secondary endpoints

The proportion of participants who achieved a response was high and similar between both groups at all visits, and most participants achieved a plasma HIV-1 RNA of <50 copies/mL by week 4 (72% in the 2DR group and 70% in the 3DR group; Figure 4). A rapid decline of viral load was observed with a median time to viral suppression of 29.0 days in both groups (Figure 4).

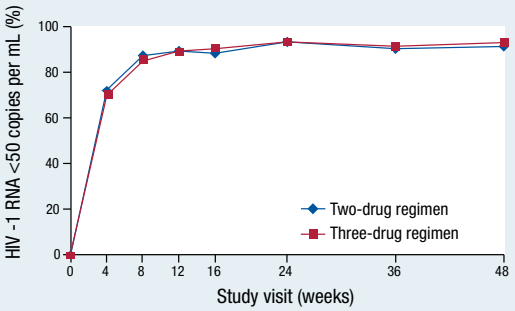

Figure 4. Snapshot analysis of the proportion of participants with plasma HIV-1 RNA of <50 copies/mL by visit in the pooled analysis of the intention-to-treat-exposed populations.[1]

Comparable virological efficacy was observed in subgroups stratified by baseline viral load (≤100 000 or >100 000 copies/mL). A lower Snapshot response in the 2DR group than in the 3DR group was observed in the subgroup of participants with baseline CD4+ count of ≤200 cells/μL (79% vs 93%, respectively). Most reasons for Snapshot failures (participants who did not have HIV-1 RNA <50 copies/mL at week 48) for this subgroup were unrelated to efficacy or treatment failure.

Both regimens were associated with low numbers of confirmed virological withdrawal through week 48 (1% of all participants); and in participants who met this criterion, neither regimen was associated with emergence of any mutations conferring resistance to integrase strand transfer inhibitors or nucleoside reverse transcriptase inhibitors.

Changes in renal and bone biomarkers favoured the 2DR. Observed lipid changes in the 3DR group, particularly triglycerides and total cholesterol-to-HDL cholesterol ratio, were significantly reduced compared with the 2DR group

Tolerability analysis

No unexpected tolerability or safety findings were observed (Table 1). Fewer drug-related adverse events occurred with the 2DR than with the 3DR, which was mainly explained by fewer episodes of grade 1 nausea in the 2DR arm.

Comparable rates of adverse events related to suicidal ideation and behaviour were observed across the two arms.

Changes in renal biomarkers favoured the 2DR. Increases in bone turnover biomarkers were noted in both treatment groups at week 48; the 2DR group had a smaller increase than the 3DR group. Total cholesterol, LDL cholesterol, and total triglycerides increased from baseline to week 48 in the 2DR group and decreased in the 3DR group, with a significant between-group difference for each parameter. HDL cholesterol had a significantly greater increase in the 2DR group than in the 3DR group. Small decreases in total cholesterol-to-HDL cholesterol ratio were observed, and this decrease was significantly greater in the 3DR group compared to the 2DR group.

EXPERT COMMENTARY ON SECONDARY ENDPOINTS

The result that proved most controversial when the results of this study were presented for the first time (at the International AIDS Conference in Amsterdam in July 2018) was that for the virological efficacy in the subgroup of participants with a CD4+ T-cell count ≤200 cells/μL at baseline. While 93% of the 3DR participants had plasma HIV RNA <50 copies/mL after 48 weeks, only 79% had plasma HIV RNA <50 copies/mL in the 2DR. At first blush this looks like a clear case of the 2DR failing more often than the 3DR. However, there are a couple of things to consider when judging this result. Firstly, it should be noted that there were only small numbers of participants with CD4+ count ≤200 cells/μL in the study: 63 (9%) in the 2DR and 55 (8%) in the 3DR. When you have small numbers, you are more likely to get an unusual result (e.g. you may not be surprised to toss a coin 10 times and get 8 tails; however, you would be surprised to toss a coin 100 times and get 8 tails).

The other important consideration is that the study designers when they wrote the statistical plan (which is done before any data is analysed) planned to do an analysis of the results according to the reasons for the failure. When this was done it became apparent that the difference between the arms with the different result was not poorer virological efficacy with 2DR but a set of other causes that meant that participants had to be withdrawn (e.g. for treatment of viral hepatitis C, treatment of TB, treatment of Chagas Disease, participant withdrawal and loss to follow-up).

Interestingly, in those participants who did fail therapy, there was not one single ART resistance mutation found on analysis. One of the commonest fears about 2DR is that failure may be more likely to select for resistance mutations. These results and those for the SWORD studies[77,78] negate that.

EXPERT COMMENTARY ON TOLERABILITY

People receiving the 2DR reported less overall adverse events and less drug-related adverse events compared to the 3DR; however, there was no difference between arms in those who discontinued their ART because of adverse events (2% in each arm).

Changes in biomarkers of bone and renal function favoured the 2DR regimen significantly. This is no surprise as the 3DR arm contained TDF, which is known to confer unfavourable effects on kidney and bone. However, it not clear whether these biomarker changes confer a worse clinical outcome over the long-term; secondly, in countries in which TAF has become available, many PLHIV have switched to that option. The data to date suggests that TAF has a safer bone and renal adverse event profile.

Lipid changes were relevantly minor and while statistically significant are unlikely to be clinically significant. It was of some surprise that the 3DR didn't show a more beneficial lipid profile compared to the 2DR as TDF has been shown to be 'lipid friendly'.

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Table 1. Reported adverse events (pooled GEMINI-1 and GEMINI-2 analysis)[1]

	Two-drug regimen (n=716)	Three-drug regimen (n=717)
Any adverse event	543 (76%)	579 (81%)
Adverse events occurring in ≥5% of participants in either group		
Headache	71 (10%)	75 (10%)
Diarrhoea	68 (9%)	77 (11%)
Nasopharyngitis	55 (8%)	78 (11%)
Upper respiratory tract infection	56 (8%)	44 (6%)
Pharyngitis	36 (5%)	32 (4%)
Back pain	35 (5%)	31 (4%)
Nausea	27 (4%)	53 (7%)
Insomnia	27 (4%)	45 (6%)
Fatal adverse events	2 (<1%)*	0
Drug-related adverse events	126 (18%)	169 (24%)
Serious adverse events	50 (7%)	55 (8%)
Adverse events leading to permanent discontinuation of treatment or withdrawal from study	15 (2%)	16 (2%)
Adverse events related to suicidal ideation and behaviour	17 (2%)	12 (2%)

* Burkitt's lymphoma and acute myocardial infarction with possible association with drug abuse. Neither considered to be related to study medication.

Conclusions

The non-inferior efficacy and similar tolerability profile of dolutegravir plus lamivudine to a standard 3DR at 48 weeks in ART-naive adults supports its use as first-line therapy for patients with HIV-1 infection.

The GEMINI studies are the first to show the non-inferiority of a 2DR containing dolutegravir in ART-naïve individuals. In addition, these studies are the first to demonstrate non-inferior efficacy of any 2DR with a standard integrase strand transfer inhibitor-based 3DR, regardless of baseline viral load. Importantly, dolutegravir plus lamivudine was not associated with treatment-emergent mutations, suggesting a high barrier to resistance.

96-week GEMINI data will be available in late 2019. Data from the phase III TANGO trial are also anticipated; TANGO is designed to demonstrate the non-inferior antiviral activity of switching to dolutegravir and lamivudine compared to continuation of a tenofovir alafenamide fumarate-based regimen over 48 weeks in virologically suppressed subjects.

As people with HIV live longer, cumulative drug exposure becomes an important treatment consideration. Therefore, initial therapy composed of 2DRs such as dolutegravir plus lamivudine may become a key factor in management decisions.

EXPERT CONCLUDING COMMENTARY

The GEMINI study is a milestone in the history of antiretroviral development. The study has robustly demonstrated that combination ART which uses only two agents is non-inferior to conventional three-drug therapy. This result challenges the 'three drugs minimum' rule that has dominated HIV medical practice since the mid-1990s. Even more impressively, the study has not shown that virological failure of the 2DR inevitably selects for ART resistance. None of those participants who met criteria in either study arm for protocol-defined virological failure manifested resistance. 2DR was associated with less adverse events although there was no difference seen for adverse events leading to study withdrawal. Whether over the long term the 2DR will be safer than 3DR is possible but only the future can tell. The GEMINI 96-week outcome data is keenly anticipated to assure everyone that the outstanding week 48 results hold through to week 96. One issue that has arisen amongst prescribers is whether people with either transmitted or archived M184V (lamivudine or emtricitabine-associated) resistance can safely be prescribed 2DR. Evidence from an assortment of cohorts and observations suggest it might, but prospective studies to systematically examine this question are in development.

TAKE HOME MESSAGES

- People living with HIV have now been receiving ART for decades, and as they age co-morbid conditions and the need to take medications for chronic conditions will become more prevalent.
- The major clinical incentive for reducing ART components is to minimise the cumulative burden on the health of a patient receiving ART.
- The GEMINI studies demonstrate noninferior virologic efficacy for the 2DR of dolutegravir + lamivudine vs the 3DR of dolutegravir + Truvada® at week 48.
- Results show broadly consistent results for virus suppression across individuals with higher viral load (more than 100,000 copies of viral RNA per millilitre of blood plasma [>100,000 copies/mL]) and lower viral load (<=100,000 copies/mL) HIV-1 plasma RNA. Patients with the highest viral loads — over 100,000 copies/mL, seen in 20% of the study participants — saw results consistent with those in patients with fewer copies.
- No patient who experienced virologic failure in either treatment arm developed treatment-emergent resistance.
- Fewer drug-related adverse events occurred with the 2DR than with the 3DR.
- The GEMINI studies provide strong data supporting dolutegravir plus lamivudine as an effective, well tolerated option for initial treatment of people living with HIV infection.

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