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I ANTI-HIV DRUGS

A. Can high-dose dolutegravir be a rescue therapy?

Dolutegravir is a powerful anti-HIV drug sold under the following brand names:

- Tivicay – dolutegravir
- Juluca – dolutegravir + rilpivirine
- Triumeq – dolutegravir + abacavir + 3TC

Dolutegravir belongs to a class of anti-HIV drugs called integrase inhibitors. In adults who have not previously used an integrase inhibitor, the dose of dolutegravir recommended by the manufacturer, Viiv Healthcare, is 50 mg once daily as part of HIV combination therapy (ART).

Among people who have previously used integrase inhibitors and whose HIV is susceptible to dolutegravir, the recommended dose is 50 mg twice daily (for a total of 100 mg daily) as part of ART.

Dolutegravir may be taken with or without food.

Although dolutegravir is a powerful drug, in some cases, perhaps because of poor adherence, levels of dolutegravir in the blood can fall to less-than-effective levels. When this happens, HIV can develop the ability to overcome the effect of dolutegravir (and other HIV drugs). In such cases, HIV develops mutations or changes in its structure that allow it to resist dolutegravir and these changes are passed on to new copies of HIV.

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An experiment in Milan

Doctors in Milan, Italy, reported the details of five patients (four men and one woman) who had an extensive treatment history. Analyses of their blood samples found that HIV had developed the ability to resist several classes of treatment.

All patients had detectable viral loads raining from 800 copies/mL to almost 100,000 copies/mL. Two of them had extremely low CD4+ cell counts—less than 10 cells/mm^3—while the remaining three patients had between 350 and 640 cells/mm^3. Patients ranged in age from 32 to 52 years.

Doctors had extensive tests done on blood samples from the patients. This allowed them to devise what they called an "optimized background regimen" (OBR). Such regimens are individualized: They are designed to make use of the anti-HIV drugs that resistance testing suggests have at least some antiviral activity against the strain of HIV in a person.

Other tests measured the levels of drug in patients' blood samples to rule out malabsorption as a cause of treatment failure.

Taking all of this information into account, doctors decided to double the dose of dolutegravir normally prescribed for treatment-experienced people. This step was a gamble because doubling the dolutegravir dose to 100 mg twice daily has not been approved for use in any country. Furthermore, the researchers were unsure of what side effects might occur or if high-dose dolutegravir would be absorbed. Moreover, three of the five patients had previously used regimens containing dolutegravir 50 mg twice daily, but these regimens had failed.

The final regimens

Doctors prescribed optimal background therapy—usually consisting of the protease inhibitors atazanavir or darunavir, both drugs taken with a small dose of ritonavir—and Truvada (tenofovir DF + FTC). Additionally, everyone received dolutegravir 100 mg twice daily.

Results

Researchers conducted extensive blood tests once patients started taking their new regimens and found that high-dose dolutegravir was well absorbed. The concentration of dolutegravir in the blood of patients was generally about four-fold greater than what has been seen with a dose of 50 mg taken once daily.

Four out of five participants were able to achieve a suppressed viral load (less than 40 copies/mL) for nearly two years, the length of the period of observation reported by the Milan doctors.

However, the viral load of the fifth participant did not respond well to the new regimen—it remained detectable for 60 weeks, his duration in the study. The doctors noted that this person had entered the study with HIV that had a history of "extensive drug resistance." This history of resistance to treatment would likely have largely "abolished" the antiviral effects of the study regimen, the doctors noted.

In four out of five participants, CD4+ cell counts increased.

Side effects

There have been reports from some observational studies that dolutegravir is associated with what researchers call "neuropsychiatric" side effects, including the following:

- sleeping problems
- anxiety
- depression
- impaired concentration

Some of these issues have also been reported with other integrase inhibitors. However, in the present study, no neuropsychiatric or serious side effects occurred.

Bear in mind

The present study is very interesting and explores a novel high-dose regimen of dolutegravir. However, the number of participants was very small and the results from the Italian study cannot be generalized to other HIV-positive patients with high-level resistance to ART. The Italian study results are promising and can be considered by other researchers, who can then plan a clinical trial to test high-dose dolutegravir-containing regimens.

REFERENCE:

Ferrari D, Spagnuolo V, Manca M, et al. Increased dose of dolutegravir as a potential rescue therapy in multi-experienced patients. *Antiviral Therapy*. 2019; *in press*.

B. Large French study examines neuropsychiatric side effects with integrase inhibitors

Integrase inhibitors are a class of anti-HIV drugs widely used as part of HIV combination therapy (ART) in Canada and other high-income countries. Integrase inhibitors are used because of at least the following reasons:

- the amount of HIV in the blood usually falls relatively quickly with their use
- they are generally well tolerated
- they tend to have few drug interactions

The leading integrase inhibitor is the drug dolutegravir, sold under the following brand names:

- Tivicay – dolutegravir
- Juluca – dolutegravir + rilpivirine
- Triumeq – dolutegravir + abacavir + 3TC

Dolutegravir was first approved in high-income countries around 2013. Starting in 2016, reports emerged of dolutegravir-associated side effects, including the following:

- sleeping problems
- anxiety
- depression
- problems with concentration

This cluster of problems is generally referred to as "neuropsychiatric" side effects by researchers and doctors. In the initial reports about these problems with dolutegravir, the neuropsychiatric side effects seemed relatively common and, in some cases, seemed to particularly affect women. However, the reports largely came from datasets that may have had unmeasured factors that caused inadvertent bias when drawing conclusions. Nonetheless, it should not be surprising that dolutegravir can cause such side effects in a minority of people, as similar side effects have been reported with other integrase inhibitors.

In France

A team of scientists in France has conducted the largest prospective study to date about the use of integrase inhibitors and their potential for being associated with neuropsychiatric side effects. The scientists scoured data from more than 21,000 HIV-positive people from 18 major clinics in France. The team focused on people who were using integrase-inhibitor-containing regimens for the first time. These regimens were initiated between 2006—when the first integrase inhibitor (raltegravir; Isentress) became available—and the end of 2016.

The distribution of integrase inhibitors among study participants was as follows:

- dolutegravir – 6,274 people
- elvitegravir (in Genvoya and Stribild; the vast majority of people who used elvitegravir would have used the formulation called Genvoya) – 3,421 people
- raltegravir – 11,520 people

The average profile of participants upon entering the study was as follow:

- age – 49 years
- 72% men, 28% women
- CD4+ cell count – 500 cells/mm^3
- viral load – less than 40 copies/mL

Most participants who took dolutegravir (66%) also took abacavir + 3TC, as these drugs are co-formulated with dolutegravir in one pill (Triumeq). People who took other integrase inhibitors used them mostly with the combination of tenofovir DF + FTC (sold as Truvada and available in generic formulations).

Results

The French scientists found that the following proportions of participants who were currently taking the following integrase inhibitors had experienced neuropsychiatric issues prior to using integrase inhibitors:

- dolutegravir – 5%
- elvitegravir – 3%
- raltegravir – 10%
- As the study was large, all differences reported below were statistically significantly; that is, not likely due to chance alone.

Overall, about 35% of all participants discontinued taking an integrase inhibitor. The proportions of people who discontinued each regimen is as follows:

- dolutegravir – 13%
- elvitegravir – 20%
- raltegravir – 51%

It is important to bear in mind that raltegravir is generally well tolerated. In the present study, many raltegravir users discontinued their use of this drug for single-tablet regimens (Genvoya, Stribild or Triumeq), as raltegravir was not co-formulated with other drugs.

Here are the proportions of people who discontinued each regimen because of neuropsychiatric effects:

- dolutegravir – 2.7%
- elvitegravir – 1.3%
- raltegravir – 1.7%

Unlike smaller studies done in the past, the present French study found no increased risk of experiencing neuropsychiatric effects because of the following factors:

- age
- gender
- use of abacavir + 3TC

An unexpected result

The researchers found that the lower a person's CD4+ cell count prior to initiating ART, the greater the risk of them experiencing neuropsychiatric side effects. Although this association was statistically robust in their analysis, the researchers cannot explain why it occurred.

Bear in mind

The French study was not a randomized clinical trial; such a trial with more than 21,000 people would have been expensive and not feasible. Randomization is an important way to help reduce the risk of drawing biased conclusions when interpreting the results from a study. This lack of randomization led the French researchers to underscore that people who were prescribed dolutegravir in this study (vs. elvitegravir) were more likely to have the following:

- be older
- have been HIV positive for longer
- had a long history of using ART
- had previously experienced neuropsychiatric side effects from other medicines prior to the use of dolutegravir

Key points

- This prospective French study with more than 21,000 participants using integrase inhibitors will likely become the landmark study about the overall rate of neuropsychiatric side effects with this class of medicines over the next several years.
- The proportion of participants who stopped taking integrase inhibitors due to neuropsychiatric side effects was generally very low, between 1% and 3%. When it comes to the safety of integrase inhibitors, these figures are reassuring for doctors, nurses, pharmacists and patients.
- It is important to note that the French study's design cannot prove that specific integrase inhibitors mentioned in the study caused neuropsychiatric side effects.
- The scientists stated that, overall, "discontinuation for side effects was less frequent with dolutegravir than with elvitegravir." However, they noted that "discontinuation for neuropsychiatric side effects, although rare (2.7%), was more frequent with dolutegravir."
- An important point to note is that prior to initiating treatment with an integrase-inhibitor-containing regimen, between 3% and 10% of participants had previously experienced neuropsychiatric side effects.

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Cuzin L, Pugliese P, Katlama C, et al. Integrase strand transfer inhibitors and neuropsychiatric adverse events in a large prospective cohort. *Journal of Antimicrobial Chemotherapy*. 2019 Mar 1;74(3):754-760.

C. Higher levels of dolutegravir in older people not linked to side effects

Most clinical trials testing HIV drugs enroll young and relatively healthy adults. Such studies do not capture the effects of a drug in different populations, particularly people aged 60 and older. As people age, subtle changes occur in their intestines and with the molecules needed to move drugs from the intestine to the blood. Also, the functioning of the kidneys gradually declines with age and their ability to filter substances from the blood is reduced.

Looking in London

A team of scientists at hospitals and research institutes in London, England, conducted a study with people aged 60 to 79 years to assess absorption of dolutegravir as well as possible changes to sleep and cognitive functioning (thinking, memory and information processing).

The team found that the maximum levels of dolutegravir in the blood were significantly greater (by about 25%) in people aged 60 and older compared to people aged 50 and younger who had taken dolutegravir in previous studies. Interestingly, there was no significant effect of elevated levels of dolutegravir on the following:

- sleep problems
- feeling drowsy in the daytime
- fatigue
- general well-being
- neuropsychiatric side effects

On some tests, higher concentrations of dolutegravir were associated with subtle improvements in cognitive functioning.

Study details

Researchers planned the study to last for 180 days. Potential study volunteers were required to have an undetectable viral load as a result of their pre-study regimen and once enrolled were switched to the following regimen:

- Triumeq – a pill containing dolutegravir + abacavir + 3TC

This medication was taken at a dose of one pill once daily in the morning, with or without breakfast.

Participants underwent extensive blood tests and surveys about sleep and other issues on a regular basis.

Researchers enrolled 43 people. Three participants dropped out by the 28th day of the study—two of them moved overseas and the third developed sensitivity to sunlight, likely caused by the study medicines.

This left 40 people in the study whose data could be analysed. By day 180, two other participants withdrew—one because of employment in another city and the other due to sleeping problems. Doctors changed this person's regimen to a combination of raltegravir + Truvada (tenofovir DF + FTC) and he recovered.

The average profile of the 40 people upon their entry to the study was as follows:

- 39 men, one woman
- age – 66 years (participants' ages were between 60 and 79 years)
- most participants (83%) were white and the remaining people were of African, Hispanic and Asian descent
- most participants had what the study team judged as "mild" sleeping problems

The data from the present study were compared to data from a previous study of dolutegravir in 16 people who were aged 50 and younger.

Results

There were changes in sleeping problems as following:

- Four people who entered the study with a mild degree of insomnia progressed to "moderate" insomnia, according to the researchers. However, this change was not statistically significant.
- Another person who had insomnia upon entering the study had it resolve with the use of dolutegravir.

Overall, in general, there were no significant changes in assessments of thinking, memory and other cognitive processes during the study.

No serious problems or side effects developed during the study, and the researchers stated that Triumeq was "well tolerated."

Why did dolutegravir levels increase in older people?

The study team is not certain why dolutegravir levels increased by 25% in older vs. younger people. They speculated that the molecules that the body uses to help carry dolutegravir from the intestine to the blood may have increased with age. However, this needs to be confirmed by a study designed just for that purpose.

Bear in mind

The present study is a very good step forward in understanding the issue of drug levels of dolutegravir in people aged 60 and older. Other pharmaceutical companies should also conduct similar studies with their drugs in this population.

A shortcoming of the present study was its reliance on an overwhelmingly male (98%) group of participants. This needs to be addressed in a future study.

The researchers found that although the concentration of dolutegravir in the blood of people aged 60 and older was 25% greater than in people aged 50 years and younger, there were no significant increases in side effects—particularly in assessments of sleep and cognition.

REFERENCE:

Elliot ER, Wang X, Singh S, et al. Increased dolutegravir peak concentrations in people living with human immunodeficiency virus aged 60 and over, and analysis of sleep quality and cognition. *Clinical Infectious Diseases*. 2019 Jan 1;68(1):87-95.

II SUBSTANCE USE

A. Quitting smoking – impact on cancer risk

Shortly after gaining entry to the body and infecting the cells of the immune system that it encounters, HIV causes profound changes to the immune system. The initiation of potent combination anti-HIV treatment (ART) generally reduces the amount of HIV in the blood to very low levels (commonly called "undetectable"), raises the levels of CD4+ cells in the blood, and improves overall health. These benefits of ART are so profound that researchers increasingly expect that many ART users will have a near-normal life expectancy.

One of the problems caused by HIV infection is persistent inflammation and activation of the immune system. These effects of HIV are only partially reduced with ART, thus inflammation and immune activation become chronic. As cells of the immune system are distributed and can travel around the body and even spend time in different tissues/organ-systems, the inflammation and activation caused by HIV can have an impact outside of the immune system. For instance, among HIV-negative people, scientists have found some evidence that chronic inflammation may play a role in the following conditions:

- cardiovascular disease
- degenerative conditions of the brain (such as Alzheimer's and Parkinson's diseases)
- type 2 diabetes
- inflammatory diseases of the digestive tract (such as Crohn's disease)
- arthritis
- psoriasis

It is also possible that chronic immune activation in HIV infection has the potential to gradually weaken and prematurely age the immune system.

Taken together, some scientists suggest that excess inflammation and immune activation in ART users has the potential to increase their risk for the growth and development of abnormal cells, pre-cancers and cancers of the kind that are relatively common in HIV-positive people today. One such cancer is lung cancer.

Smoking tobacco

Tobacco smoking can cause many harms, including increasing the risk for lung and other cancers. Surveys have found that rates of tobacco use are relatively high among HIV-positive people. In the current era, studies have found that HIV-positive people who smoke tend to have diminished life expectancy from smoking-related complications, not from HIV.

Benefits of quitting

Among HIV-negative people, smoking cessation has been found to result in many health-related benefits, including reduced risk of lung and other smoking-related cancers and reduced risk of death. However, these benefits may take some time to appear. For instance, scientists estimate that in HIV-negative people who quit smoking it takes between five and nine years to observe a significant reduction in lung cancer risk.

Brought to you by DAD

Scientists with a large database called DAD have been collecting health-related information from HIV-positive people in Australia, Europe and the United States. DAD scientists assess this data and regularly publish reports about different outcomes of HIV-related issues. In their latest analysis, DAD scientists focused on comparing rates of cancers between people who smoked and subsequently quit and people who never smoked.

The scientists found that the risk for all cancers, including smoking-related ones, was greatest in the first year after quitting. Subsequent risk for some cancers declined, though the risk of lung cancer remained elevated five years after people had quit. To reduce smoking-related complications, the DAD scientists encourage increased efforts to deter initiation of tobacco smoking and enhanced efforts at smoking cessation among HIV-positive people.

Although DAD has about 50,000 participants, scientists focused on data from 35,442 people who had a profile suitable for the present study. These data were analysed from January 2004 to February 2016.

DAD scientists focused on the following outcomes:

- diagnosis of any new cases of cancer
- diagnosis of a first episode of lung cancer
- diagnosis of any smoking-related cancer, which were listed as: cancers of the head and neck, throat, stomach, pancreas, liver, bladder, kidney and urinary tract, colon and rectum, cervical, ovary, acute myeloid leukemia and chronic myeloid leukemia
- non-smoking-related cancers

Overall, participants were monitored for up to 10 years.

The average profile of participants was as follows:

- age – 40 years
- 73% men, 27% women
- CD4+ count – 444 cells/mm^3
- 52% of participants were on ART and most of them had a viral load that was undetectable

The distribution of participants by smoking status was as follows:

- 49% current smokers
- 21% ex-smokers
- 30% never smoked

Results

All cancers

During the first year after smoking cessation, rates of all cancers increased by 28% among smokers vs. non-smokers. Subsequently, the greater the length of time that a person had quit smoking, the lower their risk of developing any cancer.

Lung cancers

In the first year after quitting, rates of lung cancer were 19-fold higher in smokers than in non-smokers. Subsequently, the rate of lung cancer fell but was still eight-fold higher in smokers than non-smokers five years after smokers had quit. After this time point, there were not sufficient cases of lung cancer to draw meaningful conclusions.

Other smoking-related cancers

As with the other cancers, the rate of other smoking-related cancers was high in the first year after quitting, but then fell to the same level seen in non-smokers.

Cancers unrelated to smoking

DAD scientists did not find any connection between smoking and the rate of cancers unrelated to smoking.

In the first year after quitting

Research with HIV-negative people has found that rates of lung cancer are also high in the first year after quitting. The DAD scientists suggested that cancers in the present study that occurred in the first year after quitting were the culmination of tumour growth and development. However, they

also noted that other factors likely played a role in the first year after quitting.

Some, perhaps many, people in the study may have quit smoking because they were "unwell either because of their undiagnosed (subclinical) cancer or because of another condition (such as chronic obstructive pulmonary disease, or COPD), which may subsequently lead to a cancer diagnosis due to increased intensity of medical surveillance." The DAD scientists suggested that even among people without COPD who had quit smoking, there may have been more contact with the medical-healthcare system because of other illnesses. This contact could ultimately have led to the discovery of a tumour(s).

Cancer cases

The distribution of cancer in the DAD study was as follows:

- total number of cancers – 2,183 people
- number of cases of lung cancer – 271 people
- number of cases of other smoking-related cancers – 622 people
- number of cases of cancers unrelated to smoking – 1,290 people

Bear in mind

DAD scientists noted that there were only 12 cases of cancer that were diagnosed more than five years after participants had quit. This small number is insufficient to draw statistically robust conclusions about the long-term cancer risk among quitters.

DAD scientists stated that there may be other reasons that HIV-positive smokers are at elevated risk for lung cancer, such as the following:

- Levels of inflammation are elevated in HIV infection in general, and in the lungs in particular. This may increase the risk for the development of abnormal cells.
- The functioning of the immune system is partially weakened because of HIV-associated chronic inflammation and immune activation. This may impact the immune system's ability to detect and destroy cancer cells.
- Low-level production of HIV and associated proteins deep within the body, including the lungs, may contribute to an increased risk of lung cancer.

For the future

The DAD analysis was imperfect; it did not have information about the number of cigarettes smoked per day or about how many years people had been smoking before they developed cancer. Despite this, its findings are a step forward.

The results from DAD underscore the need for doctors, nurses and pharmacists to help their HIV-positive patients quit smoking. At a societal level, the DAD findings are a reminder that public health authorities and politicians need to do more to help prevent susceptible people from taking up smoking.

The DAD analysis also points to a future direction for research, care and treatment. There is a continued need to intensify awareness for lung cancer screening among smokers and ex-smokers.

As more researchers expect HIV-positive people to have a near-normal life expectancy, scientific agencies that fund research need to provide the money for long-term monitoring, so that observational studies such as DAD and smaller ones within high-income countries can continue.

Resources

Smoking, addiction and breaking free

- How to Say "I Quit"—and Mean It – *The Positive Side*
- Smoking and tobacco – Canadian Cancer Society
- How to Quit Smoking – The Lung Association
- Understanding tobacco addiction – *CATIE News*
- Varenicline—An Ontario study assesses safety in HIV-positive people – *CATIE News*
- Smoking cessation: Innovative group therapy–centered support found to double quit rate – *CATIE News*
- Danish study underscores link between heart attacks and smoking – *CATIE News*

Cancer

- Canada–U.S. study looks at age when cancer appears in HIV – *CATIE News*
- Lung cancer risk linked to immunological dysfunction and bacterial pneumonia – *CATIE News*
- Study finds shift in cancers as HIV-positive people age – *CATIE News*
- Euro-Canadian study looks at trends in liver cancer in co-infected people – *CATIE News*
- Canadian Cancer Society

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